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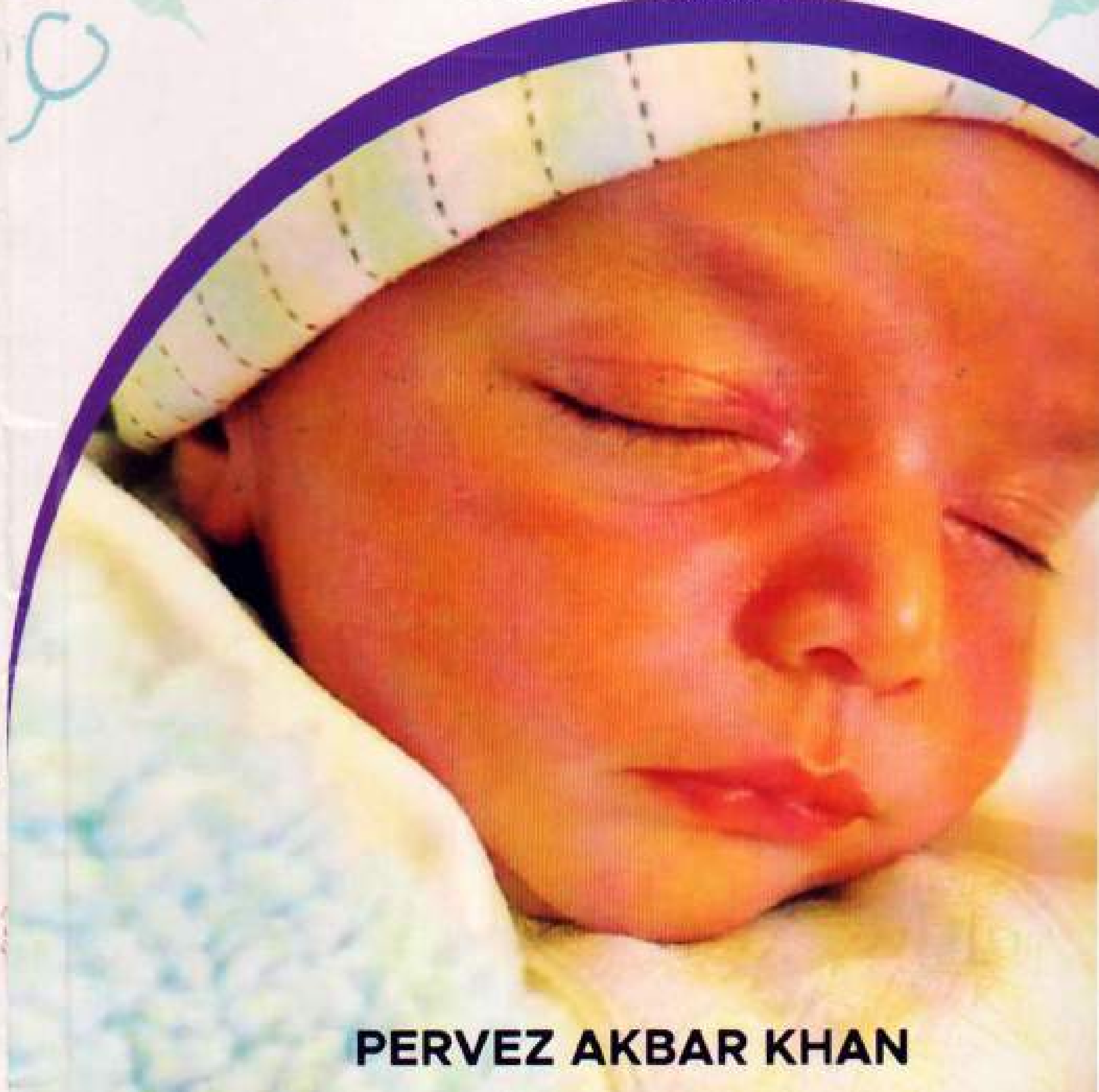
TENTH EDITION



PERVEZ AKBAR KHAN

BASIS OF PEDIATRICS TENTH EDITION

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TENTH EDITION

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Basis of Pediatrics

by

Pervez Akbar Khan

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Dedication

This book is dedicated to my parents.

PREFACE TO FIRST EDITION

This book is written for undergraduates keeping in view their special requirements and their dire need of a small book on Pediatrics. The main object of this book is to introduce the students with the elementary knowledge of Pediatrics and to enable them to prepare for the examination. It may also be useful for internee doctors who opt to work in Pediatric hospitals.

It is not meant to replace the standard textbooks of Pediatrics. Its topics have been carefully selected to include only those aspects, which are either not touched upon or discussed in detail in Medicine. This has greatly helped me to limit the volume of this book. Valuable suggestions and criticism will be greatly appreciated to this end.

I am greatly indebted to my learned teachers, Prof. Shaukat Raza Khan, Prof. S. M. Haneef, Prof. Tariq Iqbal Bhutta, Prof. Abdul Waheed Qureshi, and Prof. Fehmida Jaleel, who had great influence on me during my formative years. This book reflects the salient features of the knowledge imparted to me during these years.

My gratitude is due to Dr. M. M. Zafarullah Kundi and Dr. Shukar Elahi for providing me the material and encouragement in writing of this book. I am thankful to Dr. Muhammad Bakhsh Malik, for proof reading of this manual.

In the end, thanks are due to Mr. Karim Ullah Mazhar, for typing of this manuscript and Messer's Caravan Book Center for publishing it.

Prof. Dr. Pervez Akbar Khan
Jan. 1985

PREFACE TO TENTH EDITION

I am greatly indebted to students of Medical colleges and doctors working in children wards of different hospitals who continue to look for a book which fulfill their partial needs and at time they have to refer to textbook for further details. I still feel the students complain of studying such a large book for preparation of their exam and they require a brief version. The knowledge of pediatrics is ever expanding and I have tried to limits its volume to manageable size. For this I have curtailed many detailed explanation of different aspects and omitted many diagrams to limit its size.

In this edition I have included the recent national statistics which were available from year 2017. In addition it was a great pleasure to get help from Dr Athar Abdul Razzaq to review neonatal section and include all the recent updates available and give it a complete newer look. Similarly Dr Muhammad Imran took immense interest in updating Nephrology section and almost completely help us rewrite the section and including all the recent updates and brief essential new topics. It was a great effort on his part. I am also indebted to Dr Ghazi Khosa who spared his precious time to revise the Gastroenterology and liver diseases section. It will be pleasure to get his help in future edition also. I am extremely thankful to Dr Muhmmad Idrees who worked meticulously to read the book and brought necessary changes from scrap and added almost more then fifty paragraphs and cancel many diagrams which were unnecessary to limit the size of the book. He was also responsible to bring all the necessary changes in this new edition. It was kind of him to spare his valuable time from family life and medical profession. I shall be falling in my duty if I don't mention the name of Dr Talat Pervaiz for valuable suggestion and Dr Asif Qamar Rana to taking the responsibility to draw the diagram of growth and development and taking the responsibility to publish the book to international standards. I hope they won't let me down in this endeavor.

I shall be looking forward to students and doctors for valuable suggestion and necessary ratifications of our shortfalls. Nobody is perfect except ALLAH almighty.

Prof. Dr. Pervez Akber Khan

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CHAPTER 01

History Taking and Physical Examination

HISTORY

- History should be taken on the same pattern as in adults but it differs in the:
  1. Birth history
  2. Feeding/nutrition history
  3. Vaccination history
  4. Developmental history
- Commonly, history is taken from the mother. Some relevant points may be asked from an older child. Always listen to the mother's complaints and do not interrupt her before asking the relevant questions.
- First of all, introduce yourself to the patient/attendant.
- Do not keep looking at your watch or notes in front of you. Pay full attention to mother and child.
- During history taking, keep watching everything the child is doing and also his/her reactions.
- The name, age (or date of birth), sex of the patient and address of the parents, etc., is recorded.

PRESENTING COMPLAINTS

- Record the immediate important complaints, which led the parents to seek medical advice.
- The chief complaints should be recorded in a chronological order i.e. complaints with longest duration are mentioned first and complaints with shortest duration are mentioned last. For example:
  - Loose motions 15 days
  - Vomiting 5 days
  - Fever 2 days
  - Use the parents' own words.

HISTORY OF PRESENT ILLNESS

- It is the detailed description of the chief complaints with duration and their order of appearance.
- Enquire as to when the patient was last entirely well.
- There should be a daily documentation of events leading up to the present time, including signs, symptoms, and treatment, if any.
- Deeper inquiry about important symptoms must be made regarding:
  - Time of onset
  - Site
  - Duration
  - Frequency
  - Severity
  - Progression
  - Relieving factors
  - Exacerbating factors
  - Diurnal or seasonal variations
  - Associated symptoms
  - Contact with a case of communicable diseases e.g. tuberculosis and measles
- If symptoms point to a disturbance of a particular organ system, then ask specific questions relating to that system.
- Some general questions given below provide useful information:

General

- Weight loss
- Appetite

Cardiovascular system

- Shortness of breath on exertion
- Shortness of breath and sweaty on feeding
- Cyanotic spells (blue episodes)
- Squatting
- Chest pain or palpitations (rare)
- Fainting or syncope
- Cyanosis
- Edema

Respiratory system

- Sore throat
- Earache
- Cough (nocturnal, in relation to exercise, productive, dry)
- Wheezing (nocturnal, exercise induced)
- Frequent chest infections
- History of aspiration
- Hemoptysis

Gastrointestinal system

- Abdominal pain
- Vomiting
- Jaundice
- Diarrhea or constipation
- Blood in stool

Central nervous system

- Fits
- Syncope, dizziness
- Headaches
- Visual problems
- Numbness, unpleasant sensations
- Weakness, frequent falls
- Incontinence

Genitourinary system

- Stream
- Dysuria
- Frequency
- Nocturia, enuresis
- Incontinence
- Hematuria

Rheumatological system

- Limp
- Joint swelling
- Skin rash
- Dry mouth or mouth ulcers
- Dry or sore eyes
- Hair loss
- Cold extremities

PAST HISTORY

- Enquire about the past illness, which can have relevance to the present one or present state of health of the patient.
- Also enquire about the medications taken previously and their side effects.
- Also enquire about the infectious diseases he/she has suffered from and any complications thereof.
- History of similar complaints in the past is also helpful.
- If hospitalized, check medical records.

BIRTH HISTORY

- If the patient is a neonatal, genetic, or developmental case, more detailed birth history is required regarding miscarriages, terminations, stillbirths, or neonatal deaths.
- Birth history should be taken under following three headings:
    1. Antenatal history
    2. Natal history
    3. Postnatal history

Antenatal history (history of pregnancy)

- Health and nutritional status of the mother during pregnancy
- Whether she has taken iron, multivitamin tablets or any other drugs during pregnancy
- Enquire if mother has suffered from any illness during pregnancy, e.g. hypertension, diabetes mellitus, preeclampsia, antepartum hemorrhage or infections like rubella, urinary tract infections, syphilis, tuberculosis, etc.
- Any history of exposure to irradiation (X-rays) during first trimester
- In the past obstetric history, enquire about the problems with previous pregnancies, stillbirths or miscarriages, birth weight of previous children, prematurity and blood transfusions
- Enquire about maternal vaccination against tetanus

Natal history (history of delivery)

- Whether the delivery was conducted at home or in the hospital
- Delivery conducted by a midwife, trained health visitor or a doctor
- Technique of sterilization of instruments
- Length of gestation
- Time of rupture of membranes
- Duration of labor whether prolonged or precipitated.
- Presentation and type of delivery, i.e. spontaneous vaginal, forceps, vacuum extraction or cesarean section
- Any history of sedation or analgesia given to the mother during labor and any abnormal bleeding

Postnatal history

- Whether the child cried immediately after birth or was cyanosed and apneic
- Need for resuscitation at birth and any problem with respiration, sucking or swallowing
- Any history of convulsions, fever, jaundice or rash after birth or in the neonatal period
- Any procedures such as exchange transfusion, umbilical artery catheterization undertaken or drugs given during neonatal period

FEEDING HISTORY

- Onset of feeding, i.e. how many hours after birth first feed was given
- Whether breast-fed or bottle-fed
- Duration of breastfeeding
- At what age formula milk feeding was started.
- Composition of formula, its amount and frequency
- Any vitamin or iron supplements given
- When solids were introduced in the diet, their nature and amount
- Current diet

- Any dysmorphic features
- Pallor
- Cyanosis
- Plethora
- Jaundice
- Edema
- Gait while the child is running around

- Vital signs are monitored. These include:
  - Temperature
  - Respiratory rate
  - Pulse or heart rate
  - Blood pressure or skin perfusion
- Oral temperature measurements are used in children older than 5 years. In young children and infants, thermometer can be placed in the axilla or groin. Temperature in the axilla or groin is about 0.5°C lower and the rectal temperature is about 0.5°C higher than the oral temperature. Normal children have temperature between 36.5°C–37.5°C. Temperature is 1°C higher in infants than in older children.

Table 1.1: Normal pulse and blood pressure.

Age	Pulse (per minute)	Blood pressure (mmHg)
Newborn	120–160	35–60 mean pressure by flush method.
Up to 1 year	80–140	80/55
Up to 5 years	75–120	85/60
5–15 years	70–110	100–110/70

- Measurement of anthropometric parameters is very important. These include:
  - Height
  - Weight
  - Head circumference
  - Nutritional status (skin fold measurement)
- A comparison between actual and expected weight should be a routine in any examination.
- Length can be measured as standing height after 2 years of age and as crown-heel length in infants.
- Head circumference (occipitofrontal circumference) should be measured in all infants under the age of 2 years. Hydrocephalus should be suspected if the rate of growth of the head is greater than normal for age, weight, and sex of the infant.
- Skin fold measurements are useful in determining obesity and in identifying and following malnutrition. Skin fold callipers are applied over the mid triceps.
- Examine nails for clubbing, pitting, and splinter hemorrhages.
- Lymph nodes (cervical, axillary, and inguinal) are examined.
- Skin is examined for abnormal pigmentation, any evidence of bleeding (petechiae, bruises), perfusion, and dehydration.
- If there is any rash, observe for its site, color, number and size of lesions. Rash may be vesicles, papules, macules, petechiae, scratch marks, or ulcers.
- Genitalia are also examined.

Fontanel

Anterior closes by 9–18 months

Posterior closes by 3–6 months

Early closure: CP, hyperthyroidism Craniosynostosis

Delayed closure: Hypothyroidism, rickets, malnutrition

Head

Size, Shape

Large head:>3 SD above mean for age sex hydrocephalus

Small head:<3 SD below mean for age sex CP, Craniosynostosis, TORCH

Sutures

Doses by 6 months of age

Delayed closure hydrocephalus

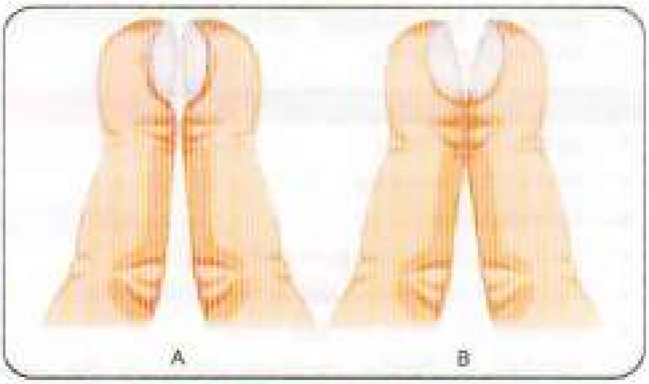


Figure 1.1: Schamroth sign: Normal (A), Clubbing (B)

DEVELOPMENTAL ASSESSMENT

- Developmental assessment is done by comparing the achievement of various milestones at various ages. (see chapter growth and development)
- Examine breasts and nipples for size and stage of development.

HEAD AND NECK

- Size and shape of the head
- Moulding
- Cephalhematoma, caput succedaneum
- Patency and state of the anterior fontanel
- Any abnormal swelling or growth in the neck

VACCINATION (IMMUNIZATION) HISTORY

- Type of vaccination given
- Age at which vaccination was started
- Number of doses given and any side effects observed. (It is important to know the absolute and relative contraindications to all vaccinations)

DEVELOPMENTAL HISTORY

- Age at which various developmental milestones are achieved.
- These are compared with the normal for this age, e.g. smiling, ability to hold the neck, sit, crawl, stand, walk, talk and control of bladder and bowel, etc. (It is important to know at least four milestones for different ages, which parents can answer easily).
- Is the development appropriate for age?
- Has there been regression of developmental milestones once achieved?

SCHOOLING HISTORY

- School name
- Class
- Progress report
- Any special needs or support
- Any missed school attendance
- Relations and behavior with other children, class fellows, and friends

FAMILY AND SOCIAL HISTORY

- Ages of the parents
- Married for how long
- Consanguinity
- Similar illness in siblings or parents
- Education, occupation and income of the parents
- Number of siblings and age range
- Number of family members living in the same house/room
- Family history of any disease, e.g. hypertension, diabetes, tuberculosis, etc.
- Type of neighborhood
- Type of water supply and arrangements for refuse disposal
- Any pets at home
- (Detailed family history is needed in case of chromosomal, hereditary, or infectious diseases)

DRUG HISTORY

- Note any medication used its frequency and dose.
- Ask about allergies.
- In a neonate or breast-fed baby, a maternal drug history is important.

PHYSICAL EXAMINATION

GENERAL PHYSICAL EXAMINATION

- Introduce yourself to the child or his/her parents.
- Ask if you may examine the child.
- Ask the child's name.
- Before examining a child while talking to the mother, inspection of the whole child for a while is very important before undressing the child.
- Sometimes, in pediatrics practice, no set routine of inspection, palpation, percussion, and auscultation is followed. Examination is by regions rather than by system. You may need to change your order of examination according to the age and behavior of the child.
- Warm your hands before starting the general physical examination.
- Position the child appropriately to facilitate the examination.
- Part to be examined should be adequately exposed. Ask mother to undress the child and help her to do so. Because the entire child is to be examined, at some time all of the clothing must be removed. This does not necessarily mean that it must be removed at the same time. Only the part that is being examined needs to be uncovered and then it can be reclothed. Except during infancy, modesty should be maintained and the child should be kept as comfortable as possible.
- Examination should be gentle and smooth. Do not lose the opportunity to examine the sleeping infant or young child. Never hurt a child or make the child uncomfortable during examination. Start the examination by the least threatening maneuvers. Initially perform those maneuvers that require the child's cooperation. Unpleasant or painful parts of the examination should be examined in last and should be explained to the child before proceeding. Pause immediately if the child becomes upset or cries.
- It is better to examine the child in close proximity to his/her parents. Child should be examined either in the mother's lap or while held over the shoulder. Older children usually are quite cooperative and they can be examined while lying in bed or sitting in the chair.
- If the child is not cooperative, distract the child with a toy.
- Look at the whole child.
- Estimate the approximate age.
- Observe:
    - Conscious level
    - Speech (appropriate for age, hoarseness, dysphasia, dysarthria)
    - General health (e.g. failure to thrive)
    - Shortness of breath

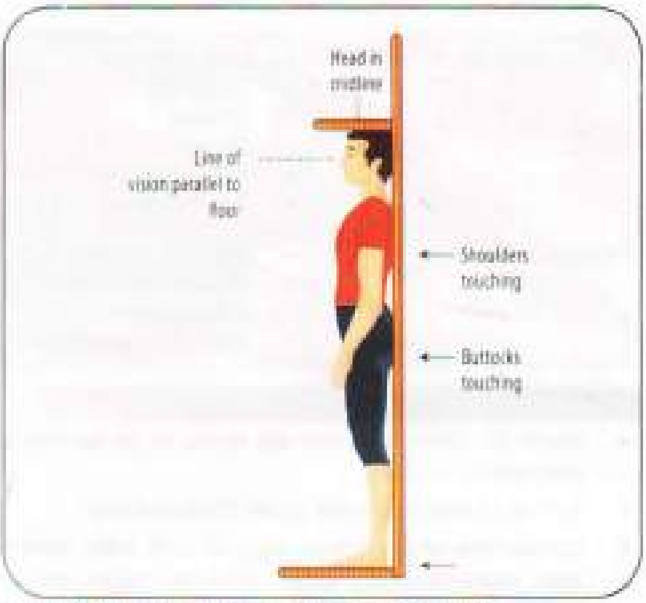


Figure 1.2: Measuring stature in children and adolescence.

Eyes

- Examine the eyes for ptosis, squint, nystagmus, subconjunctivalhemorrhage, jaundice, cataract, sticky eyes, pupillary light reflex and visual abnormalities.

Ears

- Examine the ears for any abnormality of shape, low-set ears, any wax or boils.
- Tympanic membrane is examined for congestion and perforation.
- Hearing is also checked in both the ears.

Nose

- Examine shape of the nose, depressed bridge, patency of the nostrils (choanal atresia), movement of the alaenasi and any nasal discharge.

Face

- General appearance, color, odd facies (dysmorphic features) or facial palsy is noted.

Mouth

- Note any cleft lip or cleft palate.
- Examine the lips and tongue for pallor, cyanosis, thrush or ulceration.
- Also note the number and state of teeth and condition of tonsils.

RESPIRATORY SYSTEM

Inspection

- Place the child in a sitting position and in case of an older child ask whether he or she is comfortable.
- Examine the patient from the foot end of the bed and then from the right side of the chest and comment as follows:
    - Count the respiratory rate. Respiratory rate is normally 20–40/minutes.
    - Whether the patient is breathless at rest. Note the movements of alaenasai.
    - Look at the tongue for cyanosis.
    - Type of respiration (abdominothoracic, thoracoabdominal, acidotic, etc). In children, chest cage tends to be small, respiration is mainly abdominal and breath sounds comparatively louder with longer expiration.
    - Note if there is stridor or wheeze. In stridor inspiration is prolonged than expiration. In wheezing, expiration is prolonged than inspiration. Stridor and wheeze suggests obstruction of the upper or lower airways respectively.
    - Shape of the chest (normal, barrel shaped).
    - Deformity. pectus carinatum or prominent sternum is also called pigeon chest. Pectus excavatum or depressed sternum is also called funnel chest. There may be kyphosis, scoliosis, rickety rosary, or Harrison sulcus (retracted costal cartilage, suggesting chronic conditions, either airway obstruction or left to right cardiac shunt).
    - Diminished movements on the right or left side. Also inspect for intercostal, subcostal and suprasternal recession, which indicates obstruction to air entry.
    - Grunting or sighing respiration is also noted.
    - Prominent veins, scars, or pulsations.
    - BCG scar is noted.

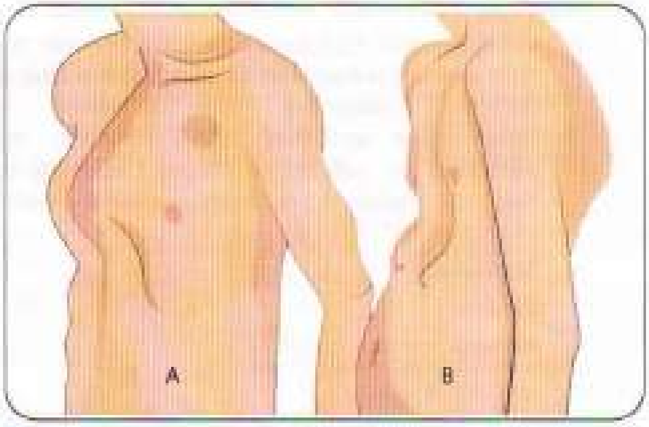


Figure 1.3: Pectus carinatum (A) and Pectus excavatum (B).

Table 1.2: Shape and deformity of the chest.

Normal	• Consolidation • Cavitation • Interstitial lung disease • Bronchial asthma (mild)
Local flattening	• Collapse • Fibrosis

Local bulging	• Pleural effusion • Pneumothorax
Barrel shaped chest	• Bronchial asthma • Chronic obstructive airway disease

Table 1.3: Normal respiratory rates at different ages.

Age	Normal range/minute
Neonate	30–60
Infant	20–50
1–4 years	20–40
5–10 years	15–25
Over 10 years	15–20

Palpation

- Following points are noted:
- Position of the trachea.
- Position of the apex beat.
- Movements of the chest with the fingers symmetrically placed in the intercostal spaces on both sides. Place the fingertips of both hands on the chest wall laterally so that thumbs meet in the midline.
- Expansion of chest. Expansion can be measured in the line of the nipples between full inspiration and expiration. This should be at least 3 cm in older child. Expansion is decreased in pleural effusion, pneumothorax, collapse, consolidation or fibrosis.
    - ○ Vocal fremitus. Feel for a difference between the right and left rather than an absolute increase or decrease. Vibrations are increased in consolidation on that side. Vibrations are decreased by collapse or pleural thickening on that side. Vibrations are absent in pleural effusion on that side.
    - ○ Tenderness
    - ○ Crepitus
    - ○ Palpable sounds

Table 1.4: Tracheal displacement.

None	• Consolidation • Cavitation • Bronchial asthma • Chronic obstructive airway disease • Interstitial lung disease
Towards lesion	• Collapse • Fibrosis
Towards opposite side	• Pleural effusion • Pneumothorax

Table 1.5: Movements of chest wall.

Reduced on affected side	• Consolidation • Cavitation • Collapse • Fibrosis • Pleural effusion • Pneumothorax
Reduced all over	• Bronchial asthma • Chronic obstructive airway disease • Interstitial lung disease

Percussion

- Warn the child what you are about to do so that he may not be terrified.
- First of all determine the upper border of liver.
- Comparison of percussion note on both sides. Percuss over supra-clavicular areas, clavicles, upper, middle, and lower chest on both sides. Percussion note is hyperresonant in asthma, pneumothorax, and foreign body aspiration. It is decreased in consolidation, collapse, fibrosis, or pleural thickening. Resonance is absent or stony dull over a pleural effusion.
- Palpate for vocal fremitus bilaterally and then percuss lightly to elicit resonance. Hyperresonant note indicates asthma, emphysema and pneumothorax, while dull note represents consolidation, collapse, fibrosis, pleural effusion or pleural thickening.

Table 1.6: Percussion note.

Tympanitic	• Over an hollow viscus e.g. empty stomach
Hyperresonant	• Asthma • Pneumothorax
Resonant	• Over normal lung
Dull	• Pulmonary consolidation • Pulmonary collapse
Stony dull	• Pleural effusion

Auscultation

- Auscultate early in the examination while the child is cooperative.
- Auscultate over supra-clavicular areas, upper, middle, and lower chest on both sides.
- Following points are noted:
    - ○ Breath sounds (intensity, character, i.e. vesicular or bronchial). If the breath sounds are harsher on one side of the chest than the other, the harsher side is normal.
    - ○ Added sounds (rhonchi, crepitations, and pleural rub).

- ○ Check vocal resonance by asking the patient to repeat one, one, one.

Table 1.7: Breath sounds.

Bronchial	• Consolidation • Cavitation • Collapse with patent bronchus • Fibrosis • Just above a pleural effusion
Diminished or absent but vesicular	• Collapse with obstructed bronchus • Pleural effusion • Pleural thickening • Pneumothorax
Vesicular	• Interstitial lung disease
Vesicular with prolonged expiration	• Bronchial asthma

Table 1.8: Causes of added sounds.

Generalized wheezing	• Asthma • Bronchiolitis
Unilateral wheezing	• Foreign body
Fine and high pitched crepitations (crackles) at lung bases	• Pulmonary edema • Fibrosing alveolitis
Coarse crepitations due to secretions	• Pneumonia • Bronchiectasis

Table 1.9: Vocal resonance.

Increased	• Consolidation • Cavitation • Collapse with patent bronchus • Fibrosis • Interstitial lung disease
Reduced	• Collapse
Reduced or absent	• Pleural effusion • Pneumothorax
Normal	• Bronchial asthma

CARDIOVASCULAR SYSTEM

- Pulse is examined and rate, rhythm, volume, and character are noted. Comparison with other pulses is important to note radio-femoral delay. Lift the arm to feel the collapsing pulse.
- Blood pressure is recorded.
- Neck veins are examined.
- Ensure adequate exposure of the precordium.
- The heart is examined while the child is lying down, sitting in the mother's lap or standing.

Inspection

- Look at the whole child.
- Following points are noted:
  - ○ Any chest deformity
  - ○ Bulging of the precordium. Anterior bulging of left chest in a thin child is due to cardiomegaly
  - ○ Any pulsations including apex beat
  - ○ Any prominent veins
- Comment on the patient's general condition (whether he/she is comfortable at rest or obviously short of breath). Look at the tongue for pallor, central cyanosis.

Palpation

- Following points are noted:
  - ○ Apex beat. Note site and character (normal, ill-sustained heaving, well-sustained heaving, tapping). Palpate the apex beat which is normally in the 4th intercostal space just inside the mid-clavicular line and note its character whether heaving or tapping, indicating left or right ventricular hypertrophy.
  - ○ Left para-sternal heave (right ventricular hypertrophy)
  - ○ Palpable heart sounds
  - ○ Thrill (palpate murmur). The accompanying murmur is by definition at least 4/6 grade.
  - ○ Palpable pericardial rub

Table 1.10: Apex beat quality.

Displaced to left	Cardiomegaly Scoliosis Pectusexcavatum
Apex on right side	Dextrocardia Dextroposition (pulmonary fibrosis, diaphragmatic hernia)
Sustained	Aortic stenosis
Forceful	Left ventricular hypertrophy

Percussion

- Percussion is sometimes required to assess cardiac enlargement, pericardial effusion or cardiac displacement.

Auscultation

- Auscultate all the four cardiac areas. Begin auscultation from the apex. Take care to palpate the right carotid pulse simultaneously for timing the various cardiac sounds.

- Always listen at the back. Innocent murmurs do not radiate to the back.
- Following points are noted:
    - Heart sounds (intensity of 1st and 2nd sounds, splitting of 2nd heart sound, 3rd and 4th heart sounds). *Presence of third heart sound or gallop rhythm indicates heart failure and friction rub indicates pericarditis.*
    - Murmurs (timing, intensity, site of maximum intensity, radiation, character, pitch, effect of respiration, effect of posture).
    - Pericardial rub

Table 1.11: Causes of heart sounds

Soft 1st and 2nd heart sounds	• Pericardial effusion
Loud 1st heart sound	• ASD • Mitral stenosis • Tachycardia
Soft 1st heart sound	• Mitral regurgitation
Loud 2nd heart sound Loud P2 Loud A2	• Pulmonary hypertension • ASD • PDA • Systemic hypertension
Soft 2nd heart sound Soft P2 Soft A2	• Pulmonary stenosis • Aortic stenosis • Aortic regurgitation
Fixed split of 2nd heart sound	• ASD
Single 2nd heart sound	• TOF • Pulmonary stenosis

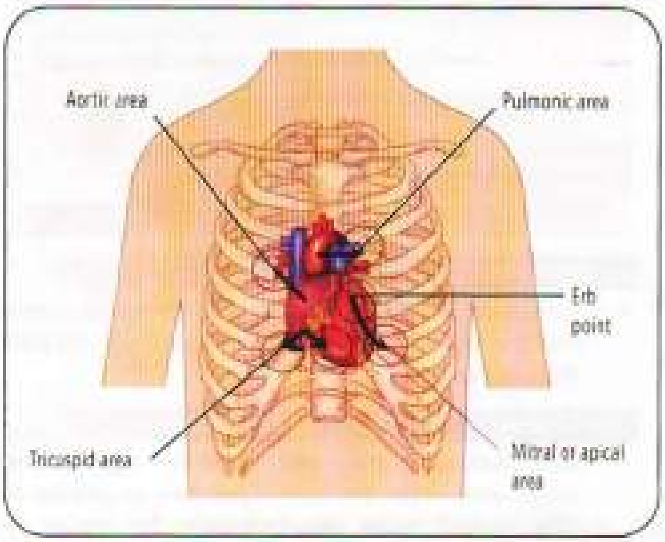


Figure 1.4: Location of auscultation areas.

Table 1.12: Characteristics of innocent (insignificant murmurs): '10S test'

1.	Symptom free
2.	Systolic
3.	Short
4.	Soft.
5.	Heard over only a Small area
6.	Split 2nd sound
7.	Sitting/standing (i.e. varies with posture)
8.	Sternal depression (benign murmurs with pectusexcavatum)
9.	No other abnormal Signs
10.	Special tests (ECG or CXR) normal

Table 1.13: Causes of murmurs

Pansystolic	• Mitral regurgitation • Ventricular septal defect
Ejection systolic	• Aortic stenosis • Pulmonary stenosis
Mid diastolic	• Mitral stenosis
Early diastolic	• Aortic regurgitation • Pulmonary regurgitation

Table 1.14: Grades of murmurs

Grade I	Murmur audible with great difficulty in a quiet room
Grade II	Murmur easily audible but not loud
Grade III	Loud murmur without thrill
Grade IV	Loud murmur with a thrill
Grade V	Very loud murmur, audible even outside the precordium
Grade VI	Murmur audible without stethoscope

GASTROINTESTINAL SYSTEM

Following parts are examined:

- Lips
- Gums
- Teeth
- Tongue
- Mucous membranes

Abdomen

- Ensure that the patient is lying flat.
- The hands should lie by his or her side with the abdomen exposed from the inframammary region to just above the genitalia. Do not expose the genitalia.

Inspection

- Following points are noted:
    - Shape of abdomen (normal, scaphoid, distended). In abdominal distension, skin is tense, shiny and underlying veins are prominent.
    - Movements of abdominal wall with respiration.
    - Visible peristalsis. In intestinal obstruction peristaltic waves may be visible.
    - Umbilicus (position, shape)
    - Scar marks
    - Striae
    - Prominent veins (site, direction of flow of blood).
    - Hernial orifices. Ask the patient to cough at this stage.
    - Pubic hair distribution

Palpation

- Ask the patient whether there is pain abdomen at any part of abdomen.
- Kneel on the floor or sit on a chair before you begin palpation. At all times look at the patient's eyes to check whether he or she feels pain.
- Begin with the superficial palpation and begin in the least tender area.
- Palpate in all four quadrants.
- Following points are noted:
    1. Light palpation to note any rigidity, guarding or tenderness.
    2. Deep palpation to note tenderness, rebound tenderness, or any mass.
    3. Palpation for the viscera including liver (also percuss for upper and lower border), spleen, kidney (bimanual palpation), and urinary bladder.
    4. Check hernial orifices.

Percussion

- Percuss for any palpable viscera or mass, fluid thrill and shifting dullness.

Auscultation

- Auscultate abdomen for 3–5 minutes for presence or absence of bowl sounds. Note their intensity.

Rectal examination

- Tell the examiner that you would like to perform a rectal examination and external genitalia.

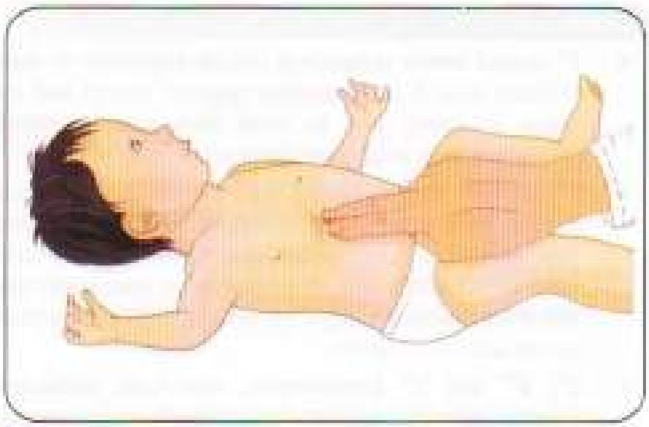


Figure 1.5: Palpation of liver.

PERINIUM AND GENITALIA

- Examine the anus for patency, fissure, prolapse, perianal dermatitis and perform rectal examination for tone of the anal sphincter, dilatation of rectum, bleeding, etc.
- Examine the genitalia for testicular descent, clitoral enlargement, ambiguous genitalia, hypospadias, phimosis, hydrocele or hernia.

CENTRAL NERVOUS SYSTEM EXAMINATION

- Neurological assessment differs in infants and children according to the functional maturation of the nervous system. It depends on the child's age and willingness to cooperate.
- In infants various neurological reflexes and developmental milestones represent the stage of development.
- The higher mental functions, state of consciousness, speech and gait are assessed routinely in children.
- In infants, great information can be gained from alertness, posture, presence or absence of movements in all four limbs, neck retraction and state of cry.
- Following points are examined:
    - Higher mental functions
    - Speech
    - Cranial nerves
    - Motor system
    - Sensory system
    - Cerebellar signs
    - Signs of meningeal irritation

Higher mental functions

- Note appearance and behavior
- Assess orientation in time and place
- Assess conscious level (Glasgow coma scale)
- Evaluate memory and general intelligence

Speech

- Note any disturbance in speech.

Cranial nerves

- **1st cranial nerve (olfactory)** can be examined in older children only. If the examiner requires you to test the sense of smell, use an odor that can be readily identified, such as soap or clove oil.
- **2nd cranial nerve (optic)** can be tested by visual fixation at a bright light in infants and visual acuity, field of vision, color vision and fundoscopy in older children. Check pupils (size, shape or inequality) and test their reaction to light (direct and indirect reaction) and to accommodation.
- **3rd, 4th and 6th (oculomotor, trochlear, abducent) cranial nerves** are tested together by noting movements of the eyes in all four directions and eliciting light reflex. Any ptosis or squint is also noted.
- **5th cranial nerve (trigeminal)** has two parts: sensory and motor. Sensations should be checked on the face and check corneal and conjunctival reflex. Motor part supplies muscles of mastication. Ask the patient to clinch the jaws and feel temporalis and masseter muscles. It can also be tested by moving the jaw from side to side. Also test jaw jerk. It is exaggerated in upper motor neuron type of lesion.
- **7th cranial nerve (facial)** can be tested by observing during crying the symmetry of face, deviation of angle of mouth to one side, obliteration of nasolabial fold and inability to close the eyes. Also, test for taste on anterior two third of the tongue.
- **8th cranial nerve (vestibulocochlear)** is tested by noting the response of the infant to a loud noise by becoming quiet if crying, turning the face towards the noise or eliciting a Moro reflex.

Table 1.15: Glasgow coma scale (GCS=E+M+V).

Pediatric Glasgow Coma Scale (PGCS)				
	>1 Year	<1 Year		Score
Eye Opening	Spontaneously	Spontaneously		4
	To verbal command	To shout		3
	To pain	To pain		2
	No response	No response		1
Motor Response	Obeys	Spontaneous		6
	Localizes pain	Localizes pain		5
	Flexion-withdrawal	Flexion-withdrawal		4
	Flexion-abnormal (decorticate rigidity)	Flexion-abnormal (decorticate rigidity)		3
	Extension (decerebrate rigidity)	Extension (decerebrate rigidity)		2
	No response	No response		1
	>5 Years	**2–5 Years**	**0–23 months**	
Verbal Response	Oriented	Appropriate words/phrases	Smiles/coos appropriate	5
	Disoriented/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
Total Pediatric Glasgow Coma score (3–15):				
Minimum score = 3 Maximum score = 15 Mild head injury = GCS 13–15 Moderate head injury = GCS 9–12 Severe head injury = GCS 8 or less				

- **9th and 10th cranial nerves (glossopharyngeal and vagus)** are tested by testing sensation on the tonsil, soft palate and pharynx. 'Ah-test', nasal twang and nasal regurgitation are assessed for integrity of vagus nerve. Taste is tested on posterior one-third of the tongue.
- **11th cranial nerve (accessory)** is tested by asking the patient to turn the face to one side against resistance and shrugging of shoulders.
- **12th cranial nerve (hypoglossal)** is tested by asking the patient to protrude the tongue and noting any deviation, tremors or wasting.

Motor system

- **Bulk and nutrition of muscles** is noted. Look for wasting or hypertrophy.
- **Muscle tone** is assessed by resistance to passive movement, feeling muscles for softness (hypotonia) or stiffness (hypertonia), shaking limbs and noting posture of extremities.
- **Power** in various groups of muscles is tested by asking the patient to execute movements against resistance.
- **Tendon reflexes:** Biceps (C5), supinator (C6), triceps (C6–7), knee (L3–4), ankle (L5–S1) and plantar reflexes are elicited. Plantar reflexes are extensor up to 18 months of age. The persistence of an extensor response beyond the age of 2 years indicates an upper motor neuron lesion. Reflexes are either absent, normal or increased. If reflexes are brisk and there are no other signs of upper motor neuron lesion, assume the reflexes as normal. Reinforcement is needed if reflexes are not elicited.
- **Superficial abdominal reflexes** and cremasteric reflex are also elicited as in adults.
- **Gait** (and muscle tone) should be observed when the child is walking.
- **Coordination** can best be checked by watching a child at play. In an older child finger-nose test or watching him dressing or undressing may help to assess coordination.
- **Involuntary movements** are noted. If present, note the type of involuntary movements and part of the body involved.

Table 1.16: Grades of power

0	No contraction
1	Flicker of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Movement against resistance
5	Normal power

Sensory system

- Testing of sensation is usually difficult in young children. If there is no neurological disease, it is better to omit testing sensation.
- Test for pain, touch, temperature, and sense of position, vibration and stereognosis.
- In infants, sensation can be tested with pinprick only.

Table 1.17: Difference between upper and lower motor neuron paralysis

	Upper motor neuron paralysis	**Lower motor neuron paralysis**
Bulk and nutrition	No wasting	Wasting
Power	Groups of muscles affected	Individual muscles affected
Tone	Increased	Decreased
Tendon jerks	Brisk	Diminished or absent
Babinski's sign	Positive	Negative
Superficial reflexes	Absent	Present
Fasciculations	Absent	Present

Cerebellar signs

- These include:
    - Nystagmus
    - Scanning speech
    - Incoordination
    - Intention tremors
    - Rebound phenomenon
    - Dysdiadochokinesia
    - Pendular knee jerk
    - Hypotonia
    - Ataxia (perform Romberg's sign)
    - Drunken gait

Signs of meningeal irritation

- These include:
    - Neck rigidity
    - Kernig's sign
    - Brudzinski's sign

NEONATAL REFLEXES

- Presence of neurological reflexes is unique in the examination of nervous system in infants.
- Primitive reflexes should disappear by 4–6 months of age. Their persistence indicates significant neuro-developmental dysfunction.

Table 1.18: Primitive reflexes.

Primitive reflexes		
Reflex	**Appears**	**Disappears**
Grasp/plantar	Birth	4–6 months
Moro	Birth	4–6 months
Rooting/sucking	Birth	3–4 months
Stepping/placing	Birth	4–6 months
Gallant	Birth	6–9 months
Tonic neck	Birth	4–6 months
Glabellar	Birth	Persists
Landau	6–8 months	15 months–2 years
Parachute	6–8 months	Persists

Moro reflex

- It is elicited by placing the infant supine upon the examining table and allowing the head (supported by the examiner's hand) to drop 10–15 degrees.
- The reflex consists of abduction and extension of arms, opening of the hands, and then adduction and flexion of the arms as in an embrace.
- It is established after about 28 weeks of fetal life and disappears at 4–6 months after birth.
- It is exaggerated or absent in a child with cerebral irritability.
- It is decreased or absent in hypotonia.
- The response is asymmetrical if there is Erb's palsy, fracture of humerus or clavicle or spastic hemiplegia.

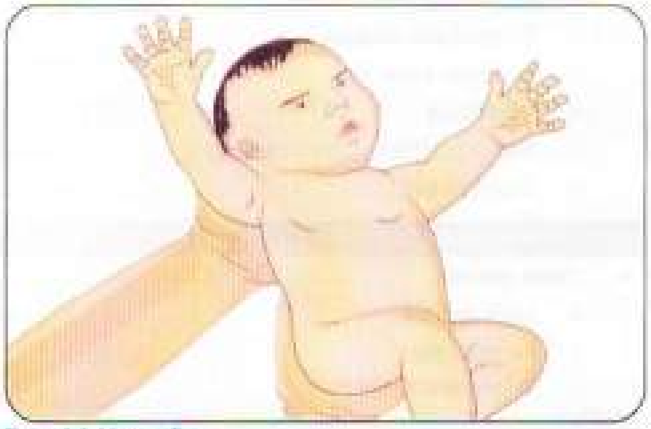


Figure 1.6: Moro reflex.

Rooting and sucking reflexes

- These are described in the chapter on infant feeding.

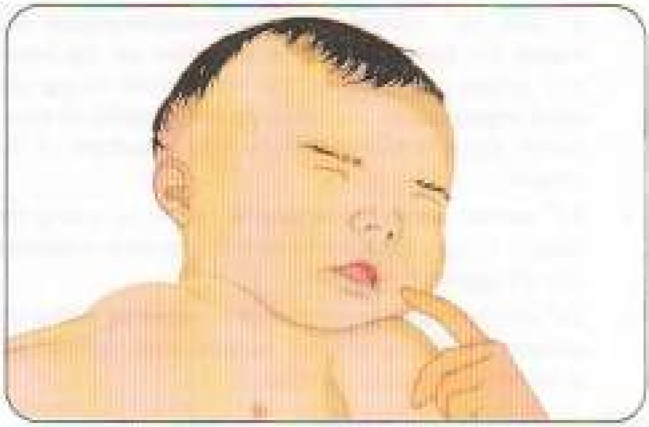


Figure 1.7: Rooting reflex.

Grasp reflex

- The palmar grasp is elicited by placing the forefinger in the palm of the infant's hand.
- The infant's fingers will rapidly flex around the examiner's finger maintaining a grip.

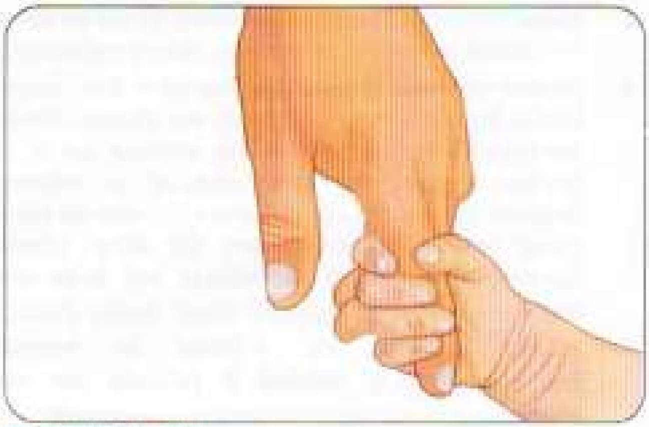


Figure 1.8: Grasp reflex.

Plantar reflex

- The plantar grasp similarly can be elicited by pressure at the head of the metatarsals of the infant's foot. The toes will flex.
- This reflex is present at birth and disappears by 4–6 months of age.

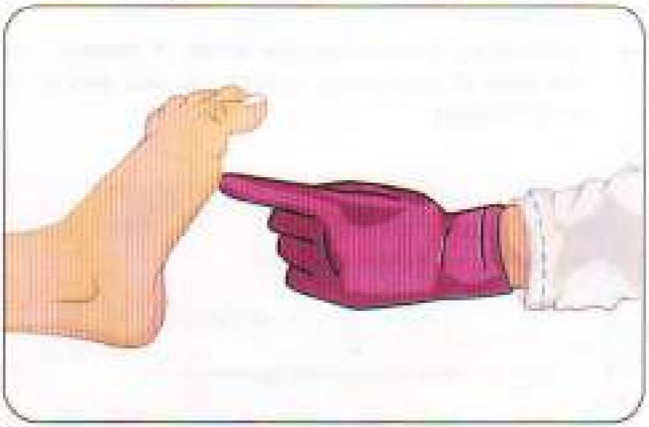


Figure 1.9: Plantar reflex.

Glabellar reflex

- A sharp tap on the glabella produces momentary tight closure of the eyes.
- It persists from birth onwards.

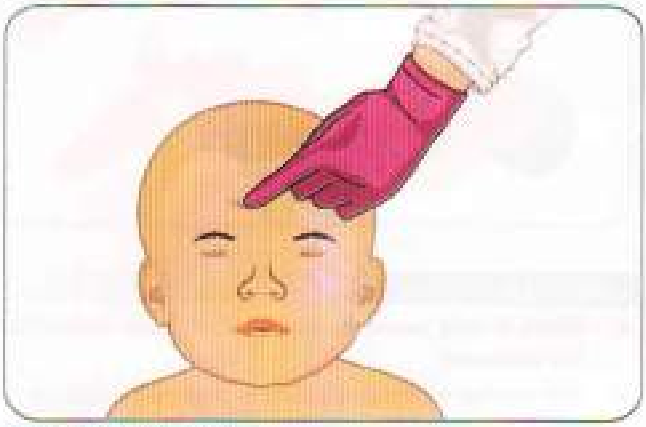


Figure 1.10: Glabellar reflex.

Doll's eye reflex

- Turn head slowly to right or left watching position of the eyes.
- In newborns the eyes move in the direction of movement.
- Normally eyes do not move with the head beyond 3 weeks of age.

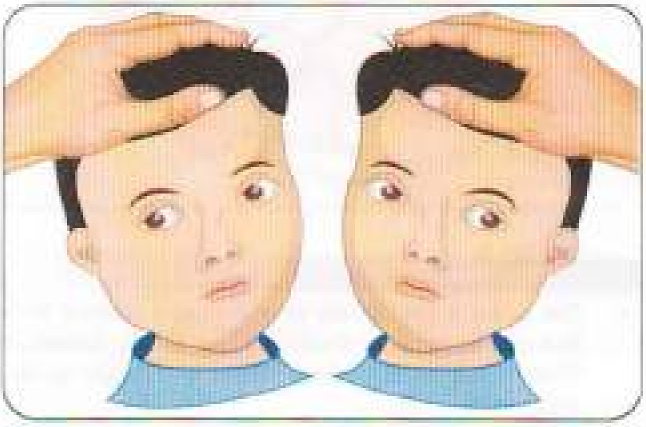


Figure 1.11: Eyes are not moving with the head in older children.

Tonic neck reflex

- It is present at birth and usually disappears at 4–6 months of age.
- With baby in supine position, this reflex is elicited by rotating the head to one side. There is extension of the arm and leg on the side to which the head is rotated and there is flexion of the arm and leg on the contralateral side.
- Normally, it persists up to 3 months of age but if it persists beyond 6 months then there is possibility of spastic cerebral palsy.

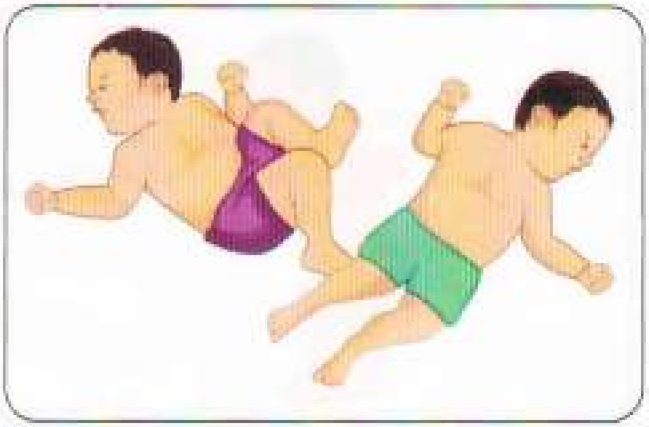


Figure 1.12: Tonic neck reflex.

Placing reflex

- The baby is held vertically with the back against the examiner; the dorsal part of one foot is moved forward so that the dorsum of the foot touches the undersurface of the edge of the table. The baby will flex the knee and bring the foot up as though trying to step on to the table.
- It is present at birth and disappears at about 4–6 months of age.

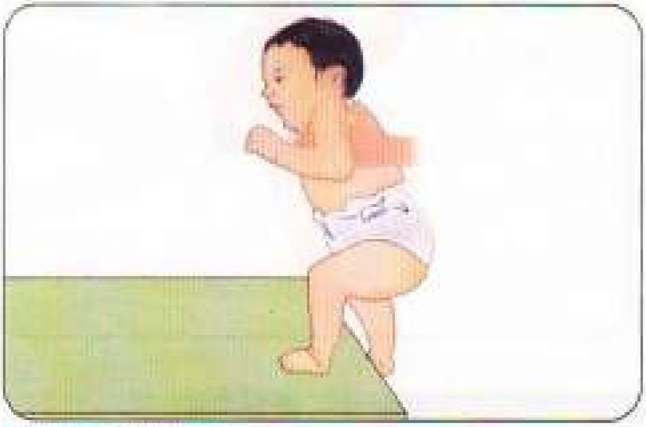


Figure 1.13: Placing reflex.

Walking (stepping) reflex

- The baby is inclined forward so that sole of one foot touches the table; the infant tries to support the weight with that leg while the other leg is flexed and brought forward. As next foot touches the table, the other leg is flexed and brought forward simulating a walk.
- Term infants will walk on the entire sole of the foot, whereas preterm infants often on their toes

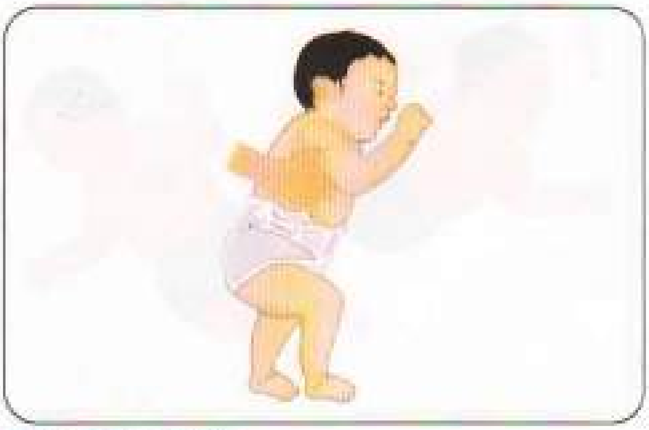


Figure 1.14: Stepping reflex.

Galant reflex

- It is elicited by holding the infant in prone position and stroking with the finger at the back parallel to the spine, first on one side and then on the other side.
- The trunk is curved towards the stimulated side.
- It is present at birth and disappears at 6–9 months.

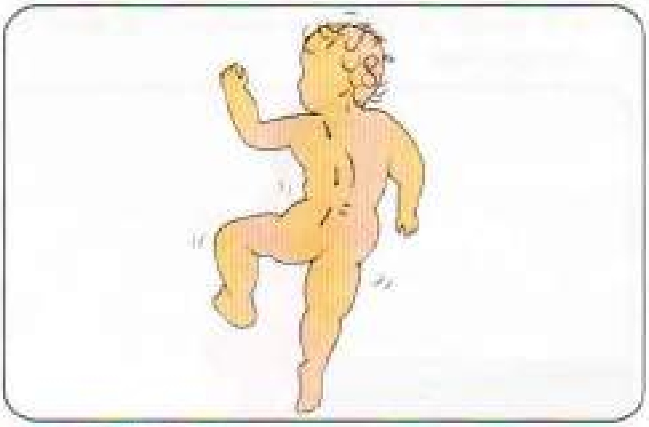


Figure 1.15: Galant reflex.

Withdrawal reflex

- The sole of the foot is pricked with a pin.
- There is rapid flexion of the hip, knee and foot as to withdraw the foot from obnoxious stimulus.

Crossed extension reflex

- In a supine infant one leg is held at the ankle and a finger strokes sole of the foot.
- The leg is flexed and adducted followed by extension of the leg so as to push the obnoxious stimulus away.
- It is present at birth and disappears at 4–6 months of age.

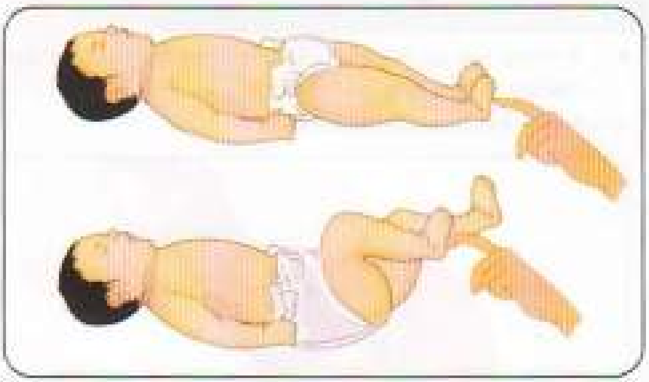


Figure 1.16: Withdrawal reflex.

Landau reflex

- Infant is held prone by placing the hands underneath the abdomen.
- The normal response consists in slight extension of the head, trunk and hips; and on flexion of the head there is flexion of the trunk and hips.
- It appears at 6–8 months of age and disappears at 15 months–2 years of age.

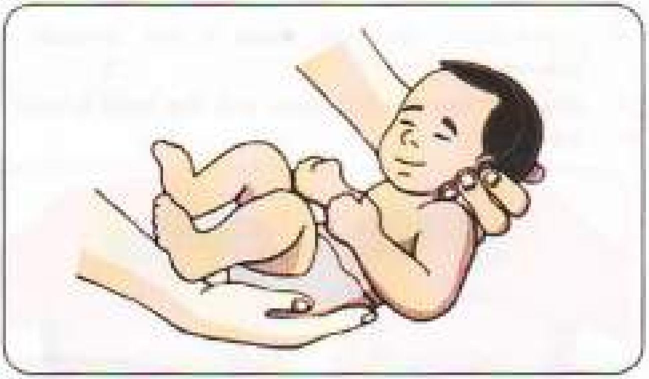


Figure 1.17: Landau reflex.

Parachute reflex

- The infant is held prone as above, and allowed to fall few centimeters by displacing the hands downward. There is extension of arms, hands and fingers as he is going to fly.
- It appears at 6–8 months of age and never disappears.

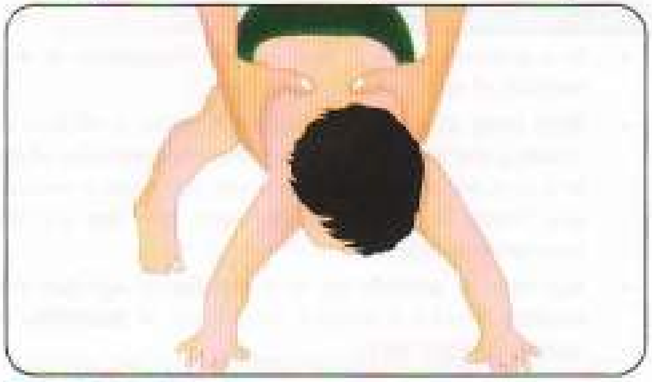


Figure 1.18: Parachute reflex.

CHAPTER 02

Growth and Development

Growth

- It is the change in size resulting from increase in the number or size of cells of the body.
- It is therefore quantitative increase in the size of the body and can be measured in terms of centimeters and kilograms.

Development

- It is the quantitative, functional maturation of the organ systems.
- It can be assessed in terms of acquisition of skills and ability to adapt to new situations as the nervous system matures.
- Growth and development are so closely related that they are usually assessed simultaneously in a patient.
- Body measurements and develop-mental landmarks provide the best and most practical means of evaluating health of the individual.
- Knowledge of growth and development is of practical importance in relation to a sick child.
- Diseases tend to have more impairment when they occur during period of rapid growth.
- Marked deviation from one percentile level to another should be regarded with suspicion. The deviation of child's own pattern of growth and development is more significant than deviation from the standard growth chart.

GROWTH

- Rate of growth is more important than actual size.
- A number of extrinsic and intrinsic factors influence the rate of growth. Some of the more important extrinsic factors are nutritional status, climate, season, illness and activity.
- Serial measurements of growth are best indicators of health. Measurement should be plotted to determine the pattern of growth and to compare them with normal standards. Graphs representing percentile distribution are particularly useful.

WEIGHT

- Body weight is probably the best index of nutrition and growth.
- Changes in weight occur before changes in other aspects of growth.
- The average weight at birth is approximately 3.2 kg (7 lbs).
- Initially newborn lose up to 10% of birth weight. It occurs due to loss of meconium, urine, physiologic edema, and less intake. Birth weight is usually regained by 10th day of age.
- The increase in weight is approximately 30 g/day or 200 g/week during first 3 months and 150 g/week up to the age of one year.
- Birth weight is doubled at 5–6 months of age, tripled at one year and four times at 2 years of age. Then there is annual increase of 5 lbs per year till puberty.
- During puberty, there is a growth spurt and rapid weight gain occurs.
- Weigh babies naked (if there is a wet nappy, weight will be changed significantly).
- Weigh older children in only their underwear.
- Make sure that the scales are properly calibrated.

Table 2.1: Weight at different ages (rule of 7).

Age	Weight (lbs)	Weight (Kg)
Birth	7	3.5
6 months	14	7.5
1 year	21	10
2 years	28	12
3.5 years	35	15
7 years	49	22
10 years	70	32.5

Table 2.2: Formulas for approximate average weight of normal infants and children.

Age	Weight (lbs)	Weight (Kg)
At birth	7.0	2.50–3.25
3–12 months	Age (month) + 11	$\frac{\text{Age (month)} + 9}{2}$
1–6 years	[Age (year) x 5]+17	[Age (year) x 2]+8
7–12 years	[Age (year) x 7]+5	$\frac{\text{[Age (year) x 7]} - 5}{2}$

HEIGHT (LENGTH)

- The average child's length at birth is approximately 50 cm. It increases by 25 cm in the first year of life.
- At 3 years of age, the average child is 3 feet (90 cm) tall; and at 4 years, 40 inches (100 cm) tall.
- Adult height is likely to be twice the height at age 2 years.
- Changes in height are slower in responding to factors, which are, detrimental to growth than the changes in weight, i.e. height is affected in chronic disorders while weight in even acute illnesses.

- Then height increases by 5 cm/year until puberty when growth spurt occurs and height increases by 9–10 cm/year for 2–3 years.
- If a child is less than 2-year-old, then measure their length instead of their height.
- A special piece of equipment is needed and two trained people in order to do this properly (infantometer).
- From 2 years onwards, child's height is measured (not length).

Table 2.3: Height at different ages.

Age	Height (cm)
Birth	50
1 year	75
2 years	85
3 years	95
4 years	100

Table 2.4: Formulas for approximate average height of normal infants and children.

Age	Centimeter	Inches
At birth	50	20
At 1 year	75	30
2–12 years	[Age (year) x 6]+77	[Age (year) x 2.5]+30

- Child's height is measured with no shoes on. Make sure that knees and heels are flat against the wall or back of the measuring frame.
- A proper standing frame is used to measure the child's height, (stadiometer).

HEAD CIRCUMFERENCE

- Measurement of head circumference serves as an estimate of brain growth.
- It increases rapidly during infancy.
- If brain size does not increase normally then head size remains small.
- Occasionally, head remains small secondary to premature union of the skull sutures, which is known as 'craniosynostosis'.
- If head circumference is small, then it should be related to overall size and weight of the body. Smaller babies tend to have smaller head. In preterm babies head is proportionately larger than the overall size of the body.
- Normally, head circumference is larger than the chest circumference at birth. But chest circumference increases in size to become equal to head circumference at one year of age and is larger thereafter.
- Then 0.5 cm increase per year occurs until 12 years (54/55 cm).

Table 2.5: Head circumference at different ages.

Age	Head Circumference (cm)
Birth	35
3 months	41
6 months	44
9 months	46
1 year	47
2 years	49
3 years	50
5 years	51

- It means brain grows rapidly initially but after age one year it slows down and increases minimally after age 5 years.
- For measurement of head circumference, a tape measure is used which is not stretchy.
- Most prominent part of the occiput to the most prominent part of the forehead is measured. Three measurements are taken.
- Record the largest of the three measurements as the head circumference.

DENTITION

- It is not a dependable milestone of development for assessment of growth because eruption of teeth is variable.
- On the average first deciduous tooth erupts at 6 months of age and eruption is complete by 2.5 years (20 teeth).
- Shedding of deciduous or milk teeth starts at 6 years and is complete by 12 years of age.

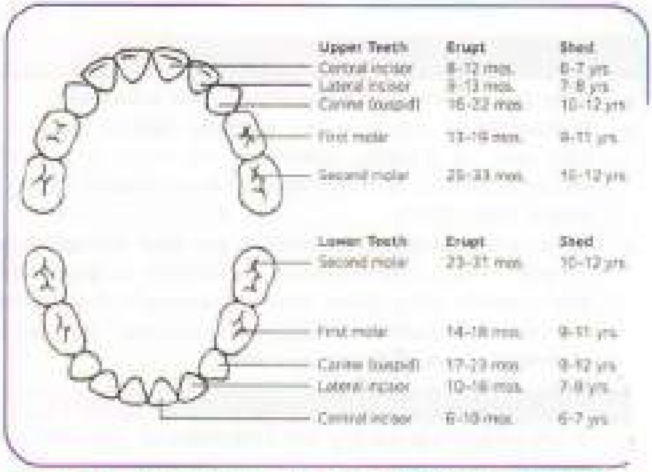

Upper Teeth
Erupt
Shed
Central incisor
8-12 mos.
6-7 yrs
Lateral incisor
9-13 mos.
7-8 yrs
Canine (cuspid)
16-22 mos.
10-12 yrs
First molar
13-19 mos.
9-11 yrs
Second molar
25-33 mos.
10-12 yrs
Lower Teeth
Erupt
Shed
Second molar
23-31 mos.
10-12 yrs
First molar
14-18 mos.
9-11 yrs
Canine (cuspid)
17-23 mos.
9-12 yrs
Lateral incisor
10-16 mos.
7-8 yrs
Central incisor
6-10 mos.
6-7 yrs

Figure 2.1: Approximate age for eruption of various teet causes of delayed eruption of deciduous teet hypothyroidism, rickets, malnutrition.

DEVELOPMENT

- Neurological development is a continuous process but it does not proceed at a constant rate.
- The development takes place in a cephalocaudal direction, i.e. control of head precedes control of arms and both precede control of the legs.
- Development is assessed under four headings:
  1. Gross motor
  2. Fine motor and vision
  3. Hearing and speech
  4. Social behavior
- It is influenced by child's maturity, illness, hunger, thirst and alertness or drowsiness.
- Premature babies cannot be expected to function at the same level as a term baby of the same age. You need to use their corrected gestational age to judge how well they are developing until they reach 2 years of age.
- Delay in acquiring certain skills is very different from a child losing the ability to do something which they could do previously. This is called regression of developmental milestones and can indicate a serious neurodegenerative condition.

NEONATE

Gross motor

Prone

- Turns head to one side, buttocks high with hip flexed, knees under abdomen, elbows flexed, hands fisted.

Supine

- Tonic neck reflex presents when head turned to one side, limbs on that side are extended and opposite side flexed (fencing posture).

Pulled to sit

- Marked head lag
- Placing and walking reflexes are present
- Palmar and plantar grasp reflexes are also present

Ventral suspension

- Head and hips are flexed
- Limbs hang downward

ine motor and vision

- Pupils react to light
- Optical closure from sudden bright light
- Doll's eye reflex present
- Eyes and head turn to diffuse light

Hearing and speech

- Cries vigorously
- Becomes alert in response to voice
- Startle reaction to sudden loud noise
- Eyes often "corner" with reflex in direction of sound source
- Engages in vocalization

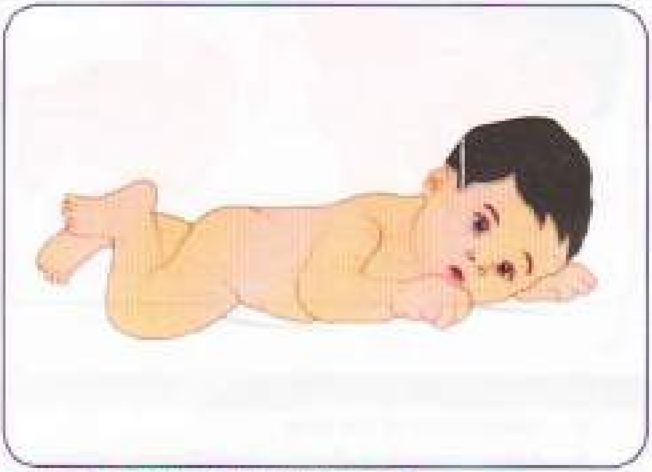


Figure 2.2: Prone. Head turned to side.

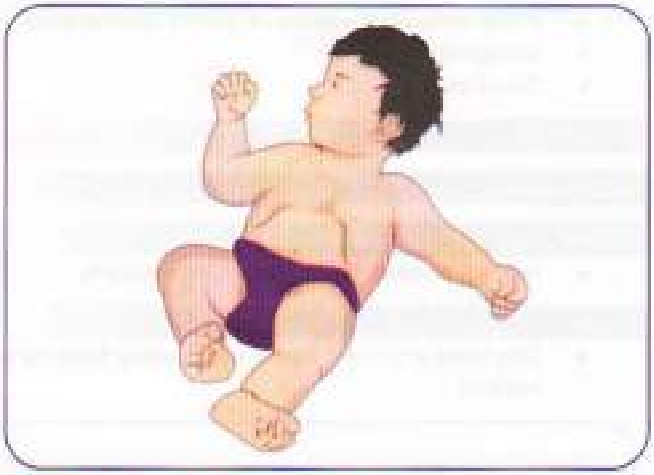


Figure 2.3: Supine. Tonic neck reflex.

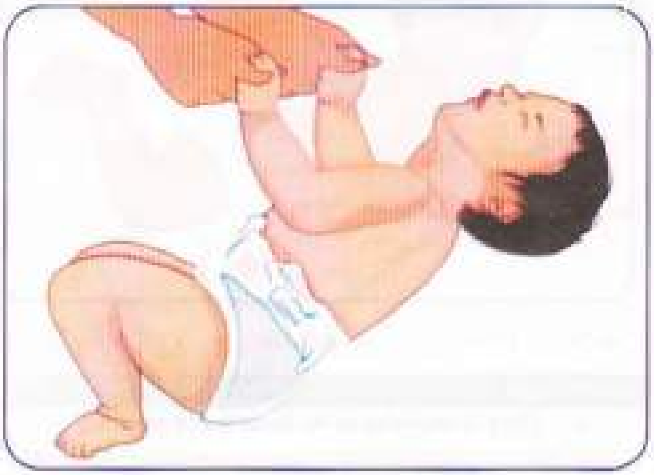


Figure 2.4: Pulled to sit. Gross head lag.

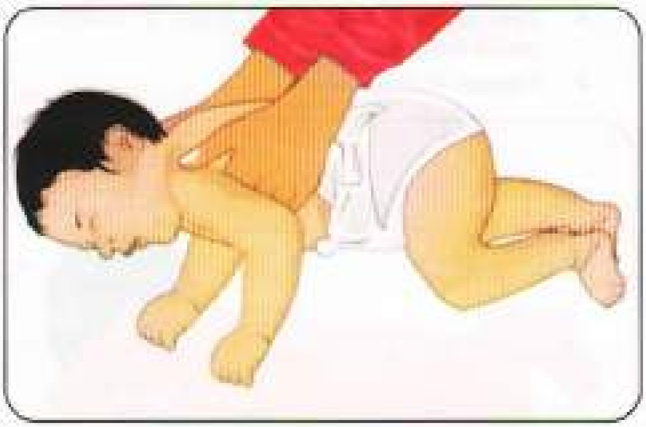


Figure 2.5: Ventral suspension.

Social behavior

- Sleeps most of the time
- Moro, rooting, sucking and swallowing reflexes are present
- Hands normally closed
- Social smile (4–6 weeks) i.e. smiles spontaneously
- Recognizes parents
- Drops toys

3 MONTHS

Gross motor

Supine

- Head in midline, limbs move symmetrically

Prone

- Lifts head and chest above couch using forearm as support.

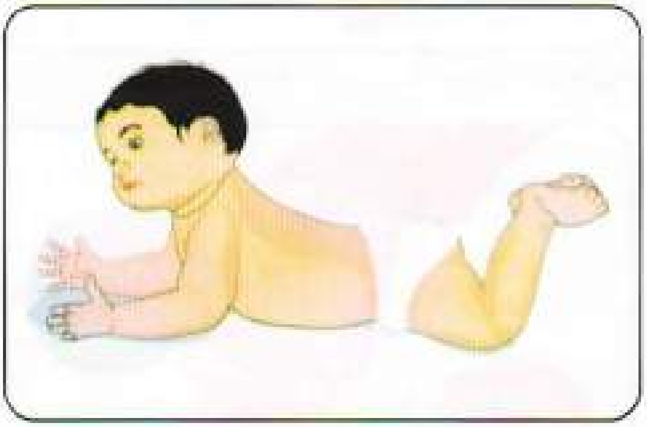


Figure 2.6: Prone. Head raised.

Pulled to sit

- Little (2 months) or no head lag (3 months)

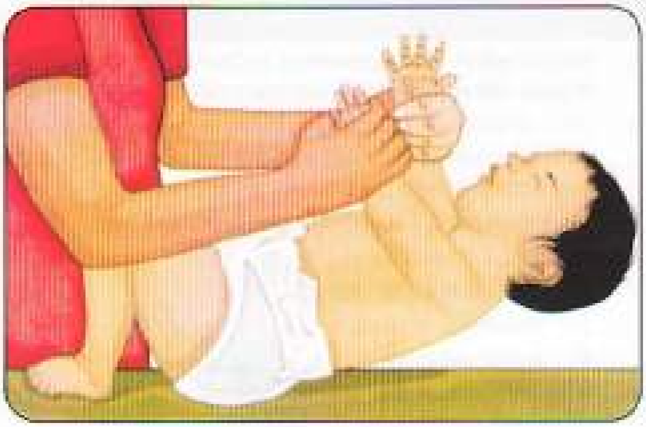


Figure 2.7: Pulled to sit. No head lag

Held sitting

- Back is straight except in lumbar region.

Held standing

- Sags at knees

Ventral suspension

- Head held well above the line of body, hips and shoulders extended.

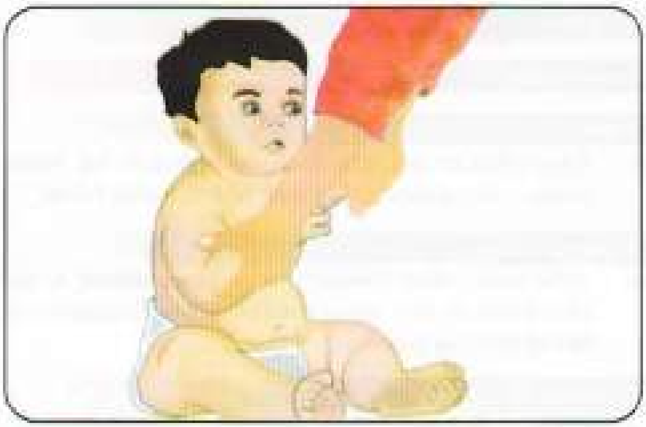


Figure 2.8: Held sitting. Back curved in lumbar region.

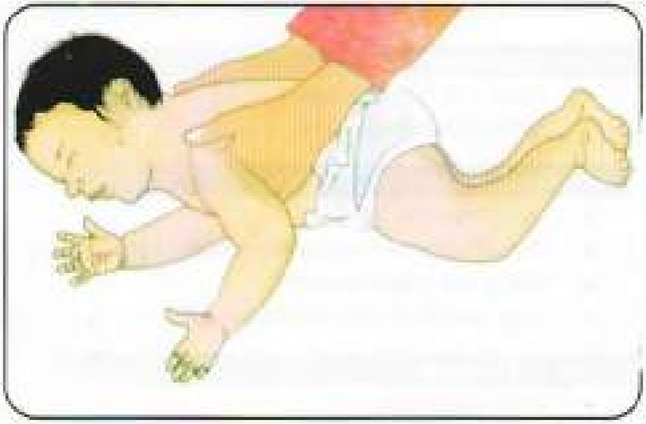


Figure 2.9: Ventral suspension. Head extended.

Fine motor and vision

- Follows light through an arc of 180 degrees (6 weeks)
- Defensive blink is present
- Regards mother's face
- Holds (grasps) rattle for a few moments
- Grasps cube–first ulnar then later thumb opposition

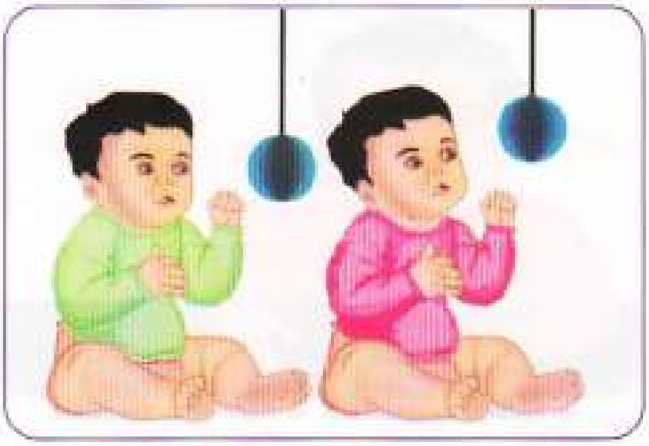


Figure 2.10: Follows a moving ball in an arc of 180°.

Hearing and speech

- Vocalizes, delighted when spoken to or pleased
- Quiets to sound of rattle or spoon in cup
- Turns to nearby voice

Social behavior

- Happy response to mother's face when feeding
- Laughs at pleasurable social contact
- Hands largely open
- Active grasp
- Anticipates food on sight

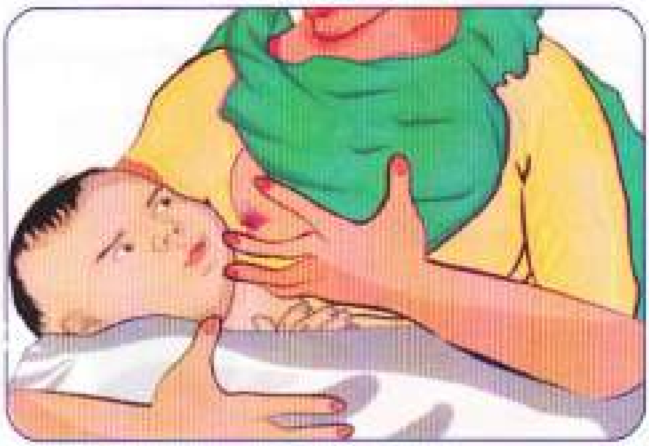


Figure 2.11: Anticipates food. Happy response to mother's face.

6 MONTHS

Gross motor

Supine

- Lifts head from pillows
- Lifts legs to vertical (5 months) and
- Grasps feet (6 months)

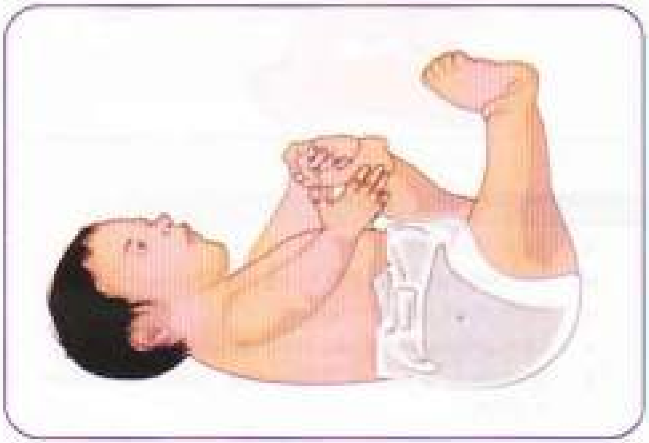


Figure 2.12: Lifts legs to vertical

Prone

- Lifts head and chest well up supporting weight on extended arms

Pulled to Sit

- Stretches out arm and raises head in anticipation
- Sits with support. Back straight
- Can roll over prone to supine (5 months) and supine to prone (6 months)

Held standing

- Takes weight on extended legs
- Downward parachute reflex present (5 months)

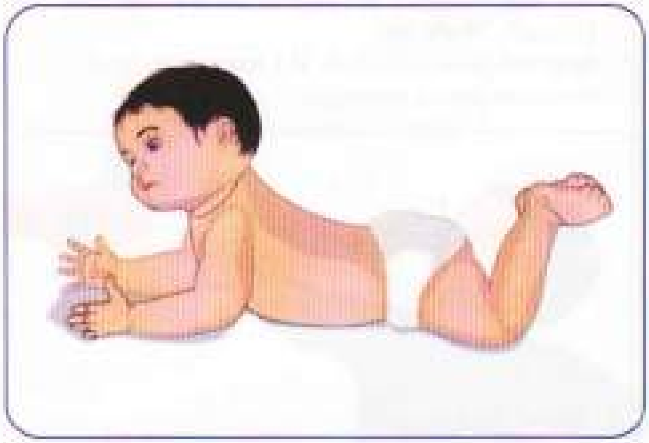


Figure 2.13: Prone. Head and chest raised.

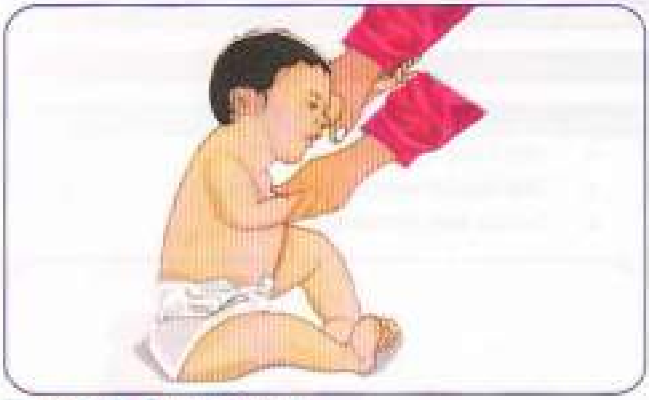


Figure 2.14 : Back is straight.

Fine motor and vision

- Reaches with one hand
- Follows dangling ball in all directions
- Both eyes move in unison
- Uses whole hand as palmar grasp
- Transfers objects from one hand to other in midline

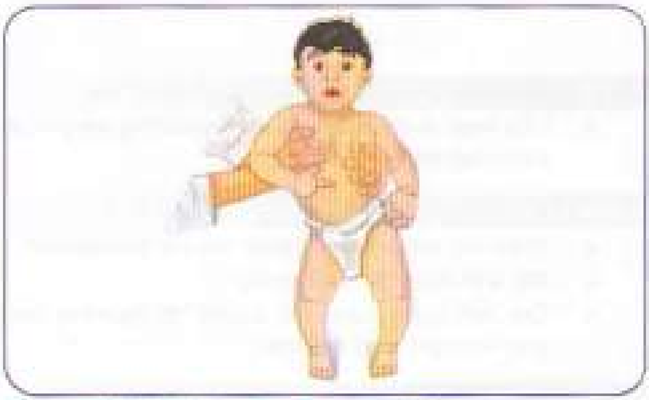


Figure 2.15: Held standing. Bears weight.

Hearing and speech

- Vocalizes tunefully in single or double "Syllables" e.g. goo, dah, ah-ah, etc.
- Responds to hearing tests at 1 foot on ear level
- Shouts to attract attention

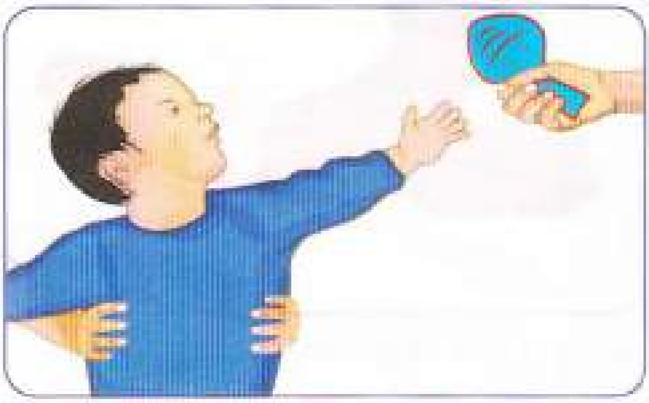


Figure 2.16: Hearing. Turns towards sound.

Social behavior

- Takes everything to mouth
- Regards hand and feet and plays with them
- Delighted response to active play
- Still friendly with strangers
- Sits alone for a short period
- Imitates "bye-bye"
- Is inhibited by the word "no"

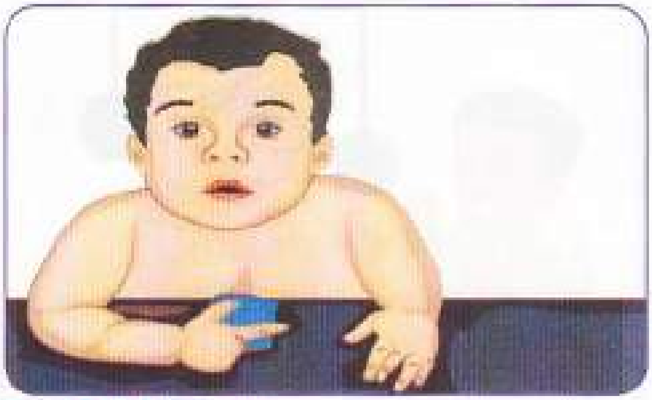


Figure 2.17: Palmer grasp.

9 MONTHS

Gross motor

- Can sit without support (8 months)
- Reach for toy in front (9 months) and
- Pivots to reach toy behind (10 months). Pulls to stand (10 months) holding on to furniture but falls with a bump
- Can crawl (10 months)
- Forward parachute obtainable from 7 months

Fine motor and vision

- Visually alert to peripheral visions
- Pokes at pellet with index finger
- Grasps string (or pick up pellet) between index finger and thumb (scissors fashion)

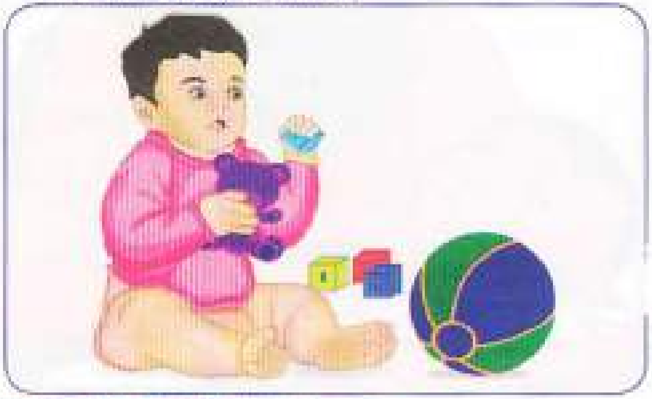


Figure 2.18: Sits without a support.

- Watches rolling ball at 10 feet
- Drops an object and looks at fallen object
- Uncovers toy (after seeing it hidden)

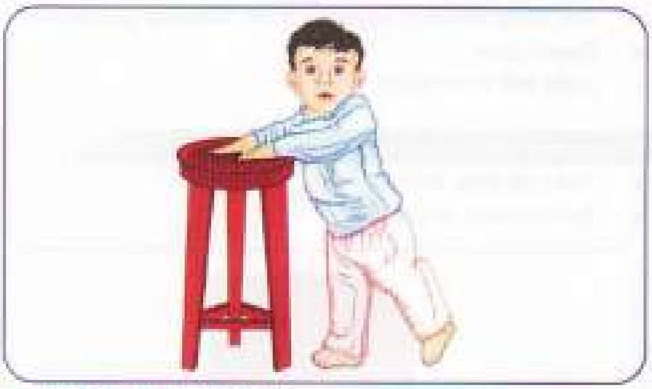


Figure 2.19: Pulls to stand.

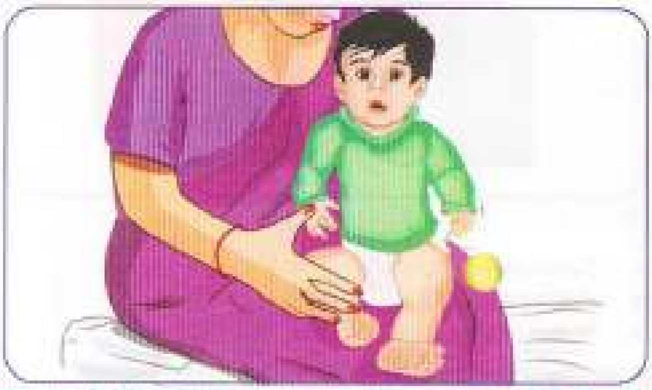


Figure 2.20: Grasps string between finger and thumb (scissors fashion).

Hearing and speech

- Localizes sounds above or below ear level at 3–6 feet
- Babbles in long repetitive "strings" of syllables (baba, dad-dad, agaga)
- Imitates adult playful sounds

Social behavior

- Holds bites and chews a biscuit
- Fear of strangers present (7 months onwards)
- Plays peek-a-boo and imitates hand clapping
- Grasps bell by handle and rings in imitation
- Finds toy, which is partially hidden
- Follows one-step verbal commands, e.g. "come here," "give it to me"

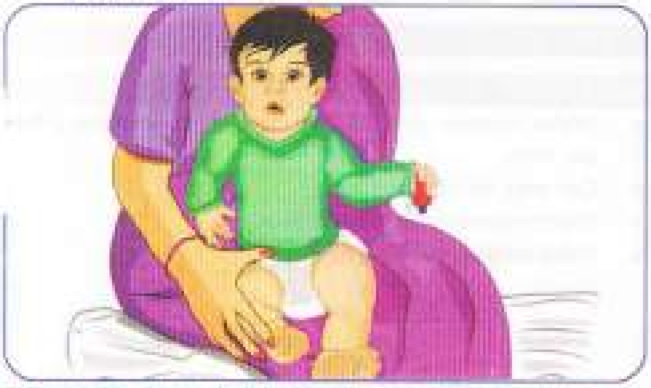


Figure 2.21: Grasps bell by handle and rings in imitation.

12 MONTHS

Gross motor

- Can walk holding on to furniture (11 months)
- Walks with one hand held (12 months)
- Walks like a bear

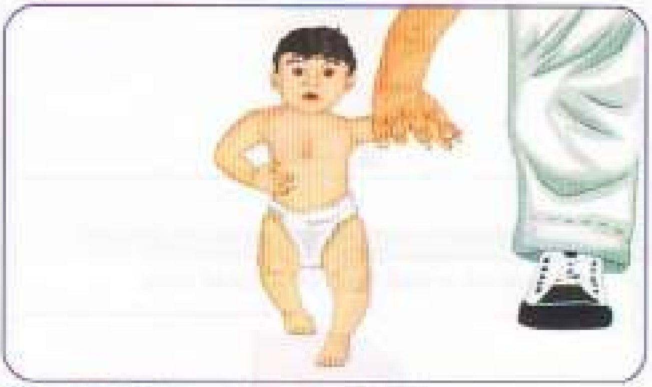


Figure 2.22: Walks with one hand held.

Fine motor and vision

- Picks up pellet with finger and thumb i.e. pincer gasp (10 months)
- Looks for hidden and fallen toys (10 months)
- Watches small toy pulled across room at 10 feet
- Holds two cubes and clicks together in imitation
- Turns pages of the book
- Releases cube into cup after demonstration
- Tries to build a tower of 2 cubes

Hearing and speech

- Knows and immediately turns to own name
- Speaks first real word. Says 2–3 words (baba, amma)
- Knows 5–6 words
- Localizes sound in a midline above head

Social behavior

- Drinks from cup with little assistance
- Helps while dressing by holding out arm
- Waves 'bye-bye' and plays 'pat-a-cake'
- Quickly finds toy hidden before his eyes
- Gives toys on request
- Points to desired objects

18 MONTHS

Gross Motor

- Walks alone with uneven steps and feet wide apart (15 months)
- Walks upstairs with one hand held, two feet per step.
- Pulls and pushes large wheeled toy.
- May run stiffly
- Throws ball

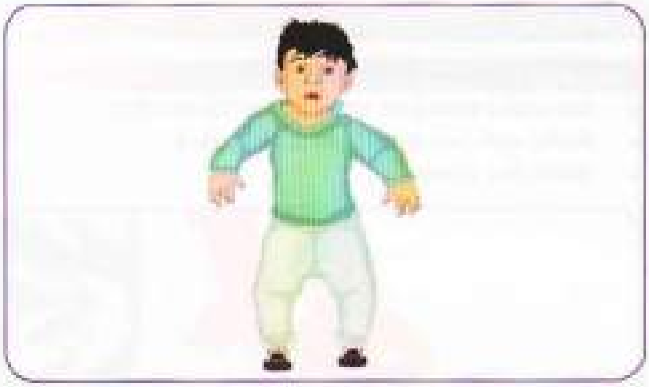


Figure 2.23: Walks alone with uneven steps.

Fine motor and vision

- Holds pencil in mid-shaft with tripod grasp

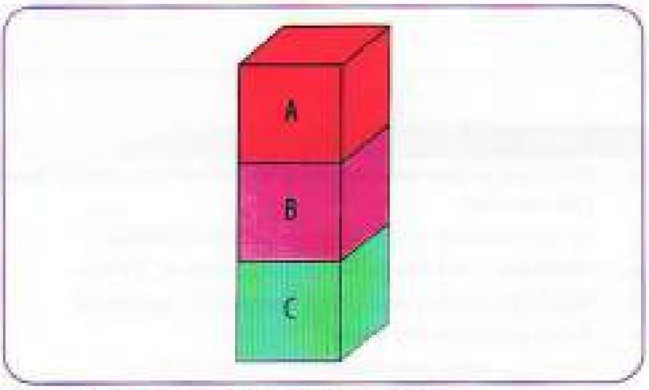


Figure 2.24: Builds a tower of three cubes.

- Builds tower of 3 cubes
- Turns several pages of book at a time
- Sits on small chair

Hearing and speech

- Uses 6–20 recognizable words and understands many more
- Obeys simple instructions, e.g. "get baba's shoes" "shut the door"
- Shows his own hair, nose, feet and eyes
- Names pictures

Social behavior

- Feeds self with spoon
- Takes off shoes and socks
- Still wets pants
- Plays contentedly alone with floor toys
- May complain when wet or soiled

2 YEARS

Gross motor

- Runs well, stops and starts safely
- Climbs on furniture, squats to play with toys on floor
- Walks up and downstairs one hand held, two feet per step
- Can jump two feet together from low step (2.5 years)
- Opens door
- Kicks ball on request

Fine motor and vision

- Picks up pins, thread
- Builds tower of six cubes

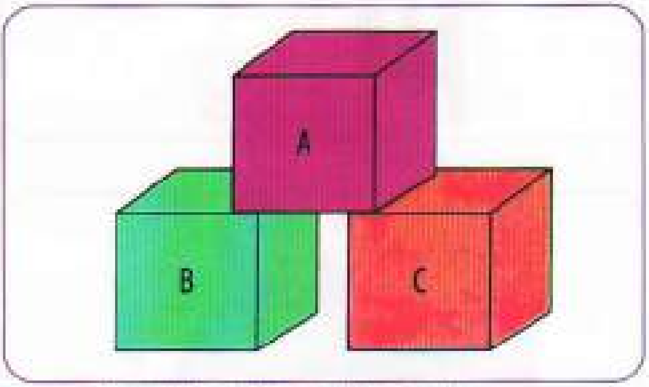


Figure 2.25: Builds a bridge with three cubes.

- Turns pages singly
- Holds pencil and scribbles
- Makes a bridge with 3 cubes

Hearing and speech

- Joins 2–3 words to form sentences
- Refers to self by name
- Constantly asking names of objects and people
- Uses 50 or more recognizable words

Social behavior

- Lifts and replaces cup safely
- Usually dry by day
- Verbalizes toilet needs.
- Imitates mother's domestic activities.
- Little comprehension of common dangers.
- Points to named objects or pictures.
- Pulls down pants or knickers at toilet but unable to replace.
- Enjoys picture books and stories (2.5 years).
- Handles spoon well.

3 YEARS

Gross motor

- Walks upstairs with alternating feet, downstairs 2 feet per step
- Can walk on tiptoe
- Stand momentarily on one foot
- Rides tricycle by using pedals

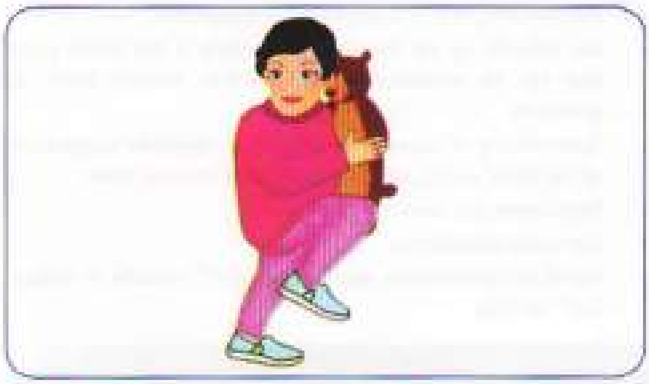


Figure 2.26: Stands momentarily on one foot.

Fine motor and vision

- Builds tower of 9–10 cubes
- Builds several bridges from a model
- Copies a circle

Speech and hearing

- Gives full name and knows age and sex
- Knows several nursery rhymes
- Counts up to 10 or more
- Counts 3 objects correctly

Social behavior

- Washes and dries hand under supervision.
- Can pull pants down and up but unable to button (dresses with supervision).
- Dry by night (toilet trained).
- Enjoys floor play with dolls, cars, bricks, etc.

4 YEARS

Gross motor

- Walks downstairs with alternating feet
- Stands on one foot 3–5 seconds
- Runs on tiptoe
- Runs and turns without losing balance
- Climbs well

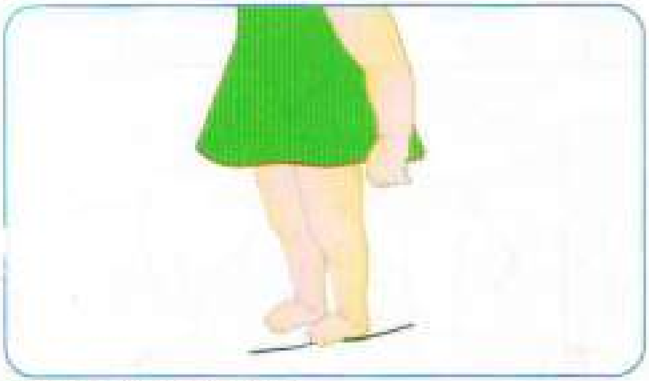


Figure 2.27: Runs on the toe.

Fine motor and vision

- Builds three steps with six cubes after demonstration
- Can copy a cross
- Copies + in imitation
- Draws a man with head, leg, and trunk
- Uses scissors to cut out pictures

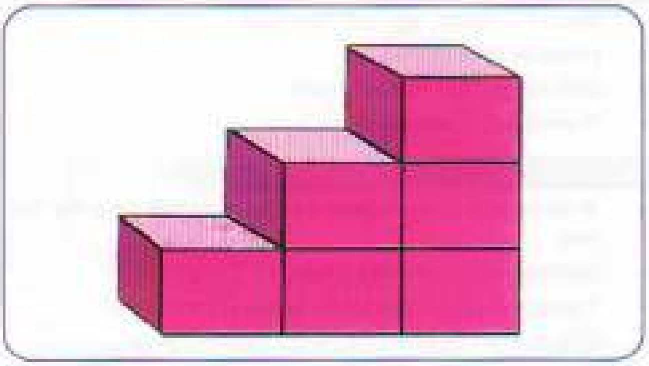


Figure 2.28: Builds three steps with six cubes.

Hearing and speech

- Gives full name and home address
- Speech grammatically correct and intelligible
- Counts up to 20 or more

Social behavior

- Washes and dries hand
- Brushes the teeth
- Can dress and undress except shoe laces
- Understands taking turns as well as sharing
- Needs companionship of other children (beginning of social interaction) but quarrels when wishes crossed
- Knows the days of the week
- Self-care at toilet i.e. goes to toilet alone but may need help with wiping
- Tells a story

5 YEARS

Gross motor

- Hops and skips on one foot
- Walks on a straight line
- Runs up and downstairs
- Stands on one foot with folded arms
- Can catch a ball

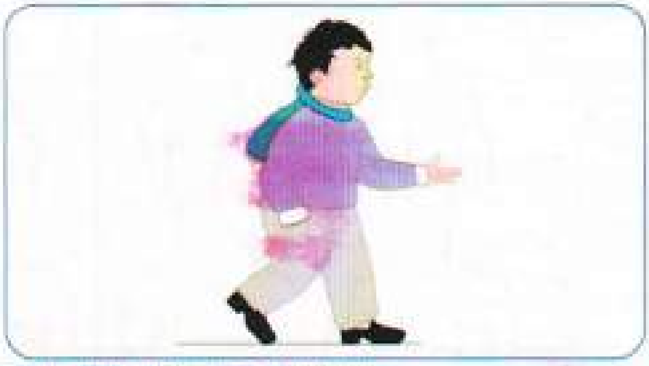


Figure 2.29: Walks on a straight line.

Fine motor and vision

- Thread large needle and sew real stitches
- Copies square and triangle at 5 years

Hearing and speech

- Gives full name, age and birthday
- Loves to listen to stories
- Defines correct nouns by use
- Names 4 colors

Social behavior

- Washes and dries hands and face; needs help for the rest
- Dresses and undresses alone
- Engages in elaborate make-believe group play
- Affectionate and helpful to younger siblings
- Knows right and left hand
- Goes to school unattended
- Good motor ability but little awareness of dangers

RED FLAGS IN DEVELOPMENT

- These indicators suggest that development is seriously delayed, and needs evaluation

Positive Indicators:
(Developmental impairment is present if the child has following activities)

- Loss of developmental skills at any age
- Parental or professional concerns about vision, fixing, or following an object or a confirmed visual impairment at any age
- Hearing loss at any age
- Persistently low muscle tone or floppiness
- No speech by 18 months, especially if the child does not try to communicate by other means such as gestures
- Asymmetry of movements or other features suggestive of cerebral palsy, such as increased muscle tone
- Persistent toe walking
- Complex disabilities
- Head circumference above the 99.6th centile or below 0.4th centile

Negative indicators:
(Developmental impairment is present if the child cannot do the following activities)

- Sits unsupported by 12 months
- Walks by 18 months (boys) or 2 years (girls)
- Walks other than on tiptoes
- Runs by 2.5 years
- Holds object placed in hand by 5 months
- Reaches for objects by 6 months
- Points at objects to share interest with others by 2 years

PUBERTY AND THE TANNER STAGES

- The Tanner scale (also known as the Tanner stages) is a scale of physical development in children, adolescents and adults
- The scale defines physical measurements of development based on external primary and secondary sex characteristics, such as the size of the breasts, genitals, testicular volume and development of pubic hair

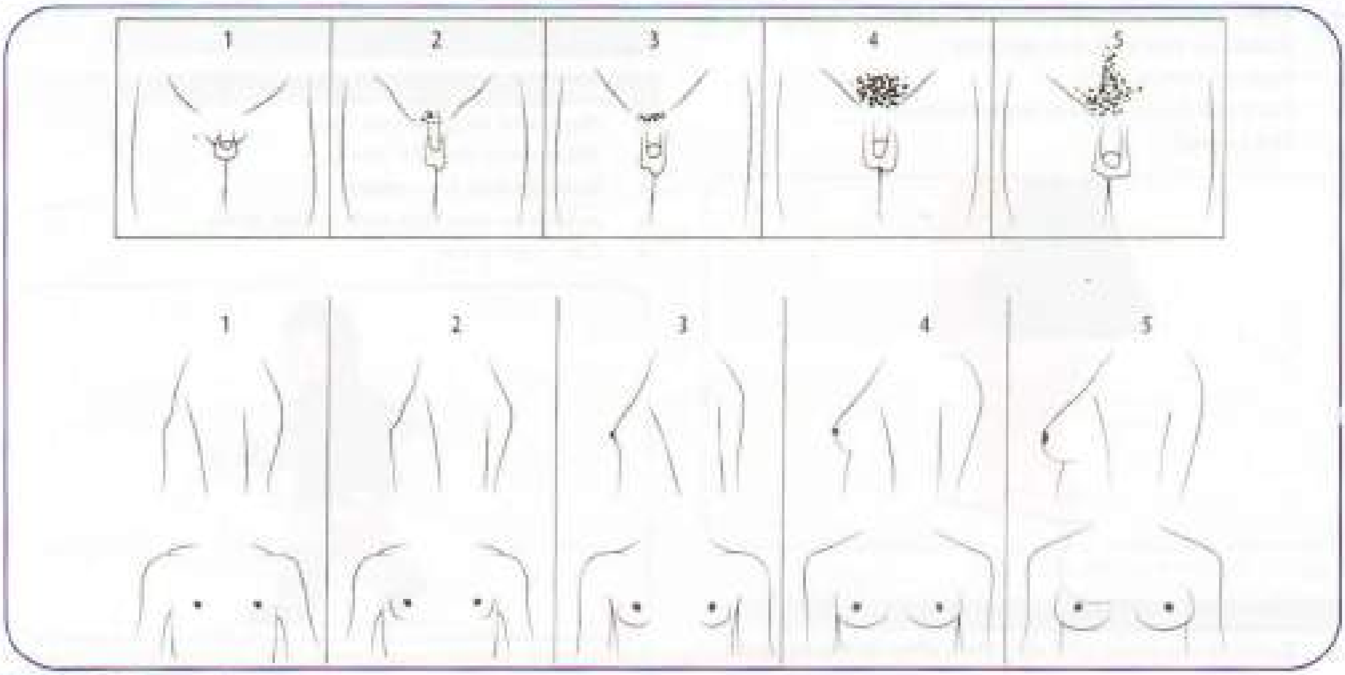


Figure 2.30: Tanner Staging

IN GIRLS

Breasts

Stage 1

- Preadolescent
- Elevation of papilla only
- Approximately between the ages of 8–11 years
- Height velocity is 5–6 cm/year

Stage 2

- Breasts bud stage
- Elevation of breasts and papilla as a small mound
- Elevation of areola diameter
- Approximately between 8–14 years of age
- Height velocity is 7–8 cm/year

Stage 3

- Further enlargement of breasts and areola
- No separation of their contours
- Approximately between 9–15 years of age
- Height velocity is 8 cm/year

Stage 4

- Projection of areola and papilla to form a secondary mound above breast level
- Approximately between 10–16 years of age
- Height velocity is less than 7 cm/year

Stage 5

- Mature stage
- Projection of papilla only, caused by recession of areola to the general breast contour
- Approximately between 12–19 years of age
- Final height reached at age 16

Pubic hair

Stage 1

- Preadolescent
- No pubic hair

Stage 2

- Slight growth of long, slightly pigmented, downy hair distributed chiefly along labia

Stage 3

- Darker, coarser, curlier hair spread sparsely over the junction of the pubes

Stage 4

- Hair is adult in type
- No spread to medial surface of the thighs

Stage 5

- Adult in quantity and quality, with no inverse triangle distribution and spread to medial thighs

IN BOYS

Genitalia

Stage 1

- Preadolescent
- Testes, scrotum, and penis are about the same size and proportion as in early childhood
- Volume of testes less than 1.6 cm
- Approximately between 9–12 years of age
- Height velocity 5–6 cm/year

Stage 2

- Scrotum and testes are enlarged, with change in texture and slight reddening of the scrotal skin
- Length of testes 2.5–3.2 cm
- Approximately between 9–14 years of age)
- Height velocity is 7–8 cm/year

Stage 3

- Growth of penis, mainly in length but also in breadth, continued growth of testes and scrotum
- Length of testes 3.3–4.0 cm
- Approximately between 11–16 years of age
- Height velocity is 8 cm/year

Stage 4

- Further enlargement of testes, scrotum, and penis, with development of glans and darkening of skin
- Length of testes 4.1–4.5 cm
- Approximately between 11–17 years of age
- Height velocity is 10 cm/year

Stage 5

- Genitalia adult in size and shape
- Length of testes 4.5 cm
- Approximately between 14–18 years of age
- Full height is reached at 18–19 years of age

Pubic hair

Stage 1

- Preadolescent
- No pubic hair

Stage 2

- Slight growth of long, slightly pigmented, downy hair distributed chiefly at the base of the penis

Stage 3

- Darker, coarser, curlier hair spread sparsely over the junction of the pubes

Stage 4

- Hair is adult in type
- No spread to medial surface of the thighs

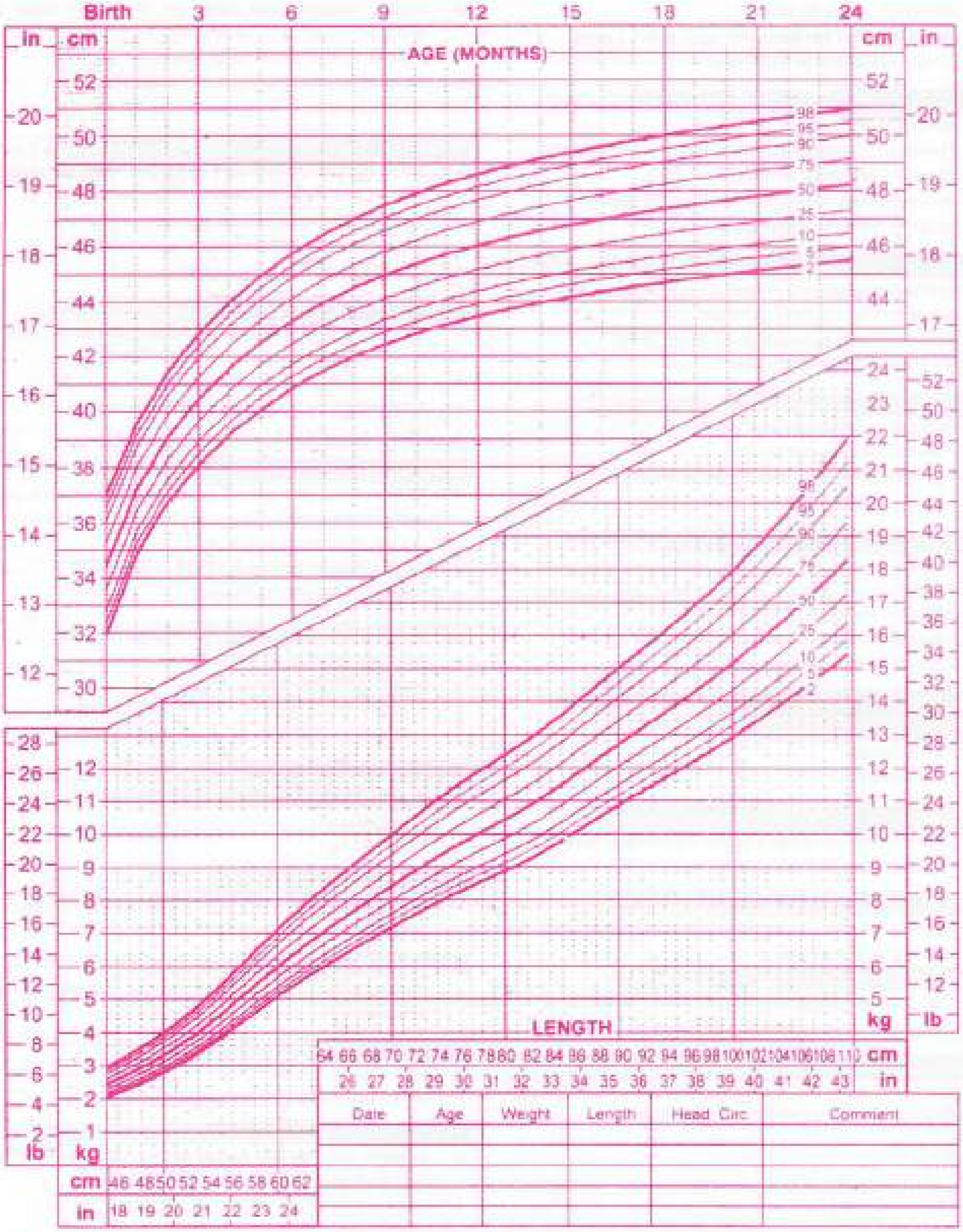
Stage 5

- Adult in quantity and quality, with no inverse triangle distribution and spread to medial thighs

Birth to 24 months: Boys
Head circumference-for-age and Weight-for-length percentiles

NAME ______________________

RECORD # ____________



Date	Age	Weight	Length	Head Circ	Comment

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

Birth to 24 months: Girls
Head circumference-for-age and Weight-for-length percentiles

NAME ______________________

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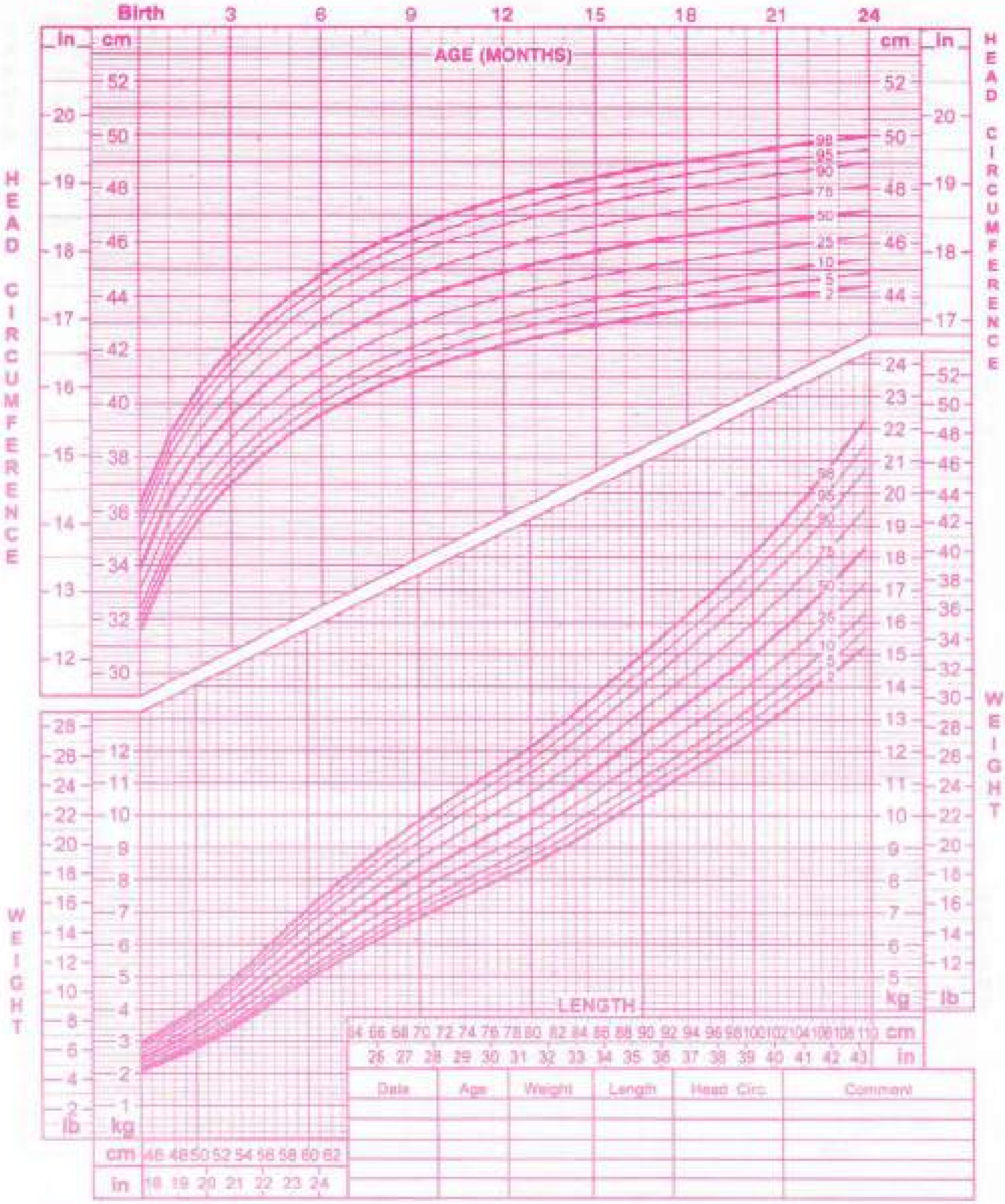

Date	Age	Weight	Length	Head Circ.	Comment

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Birth to 24 months: Boys
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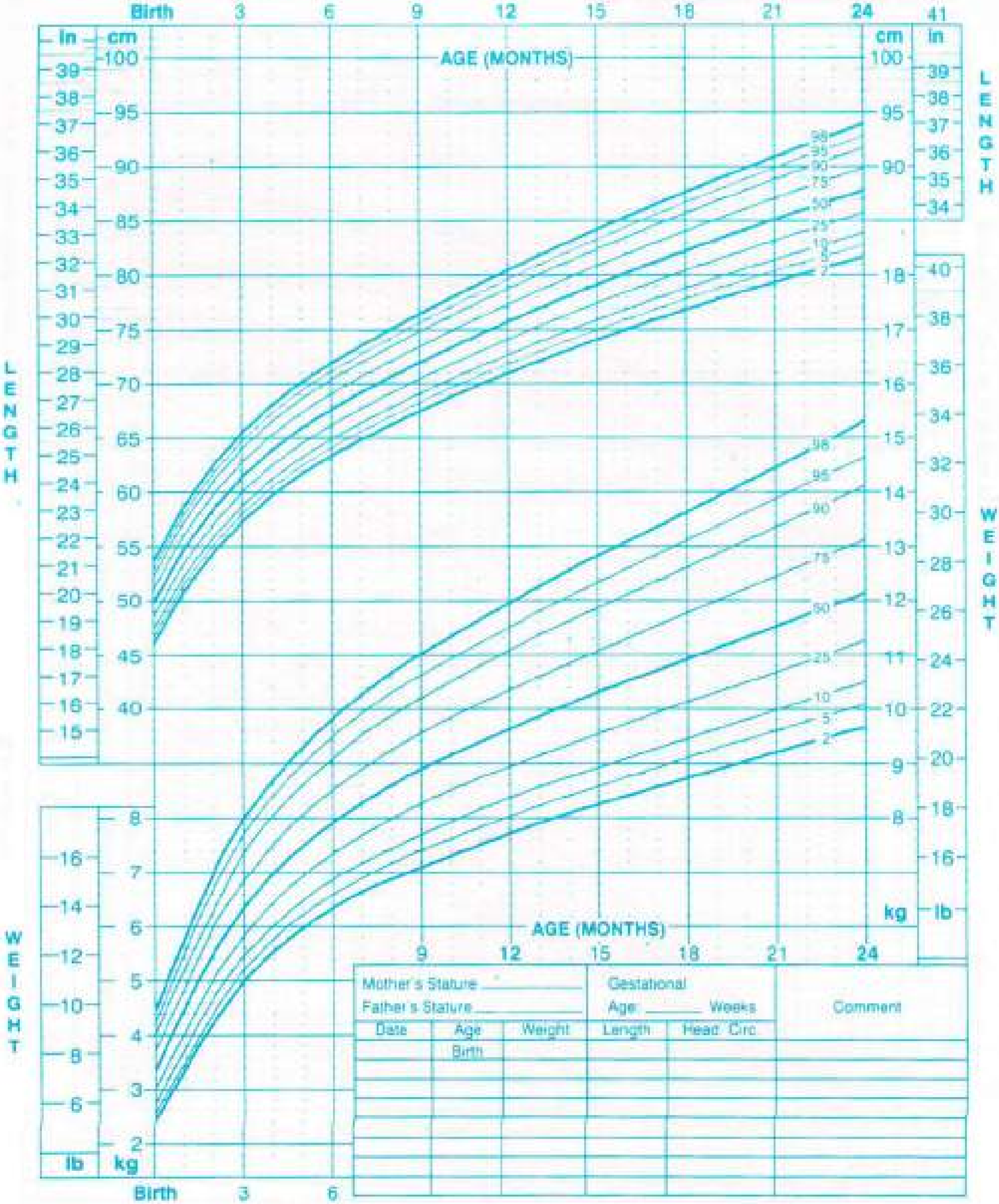

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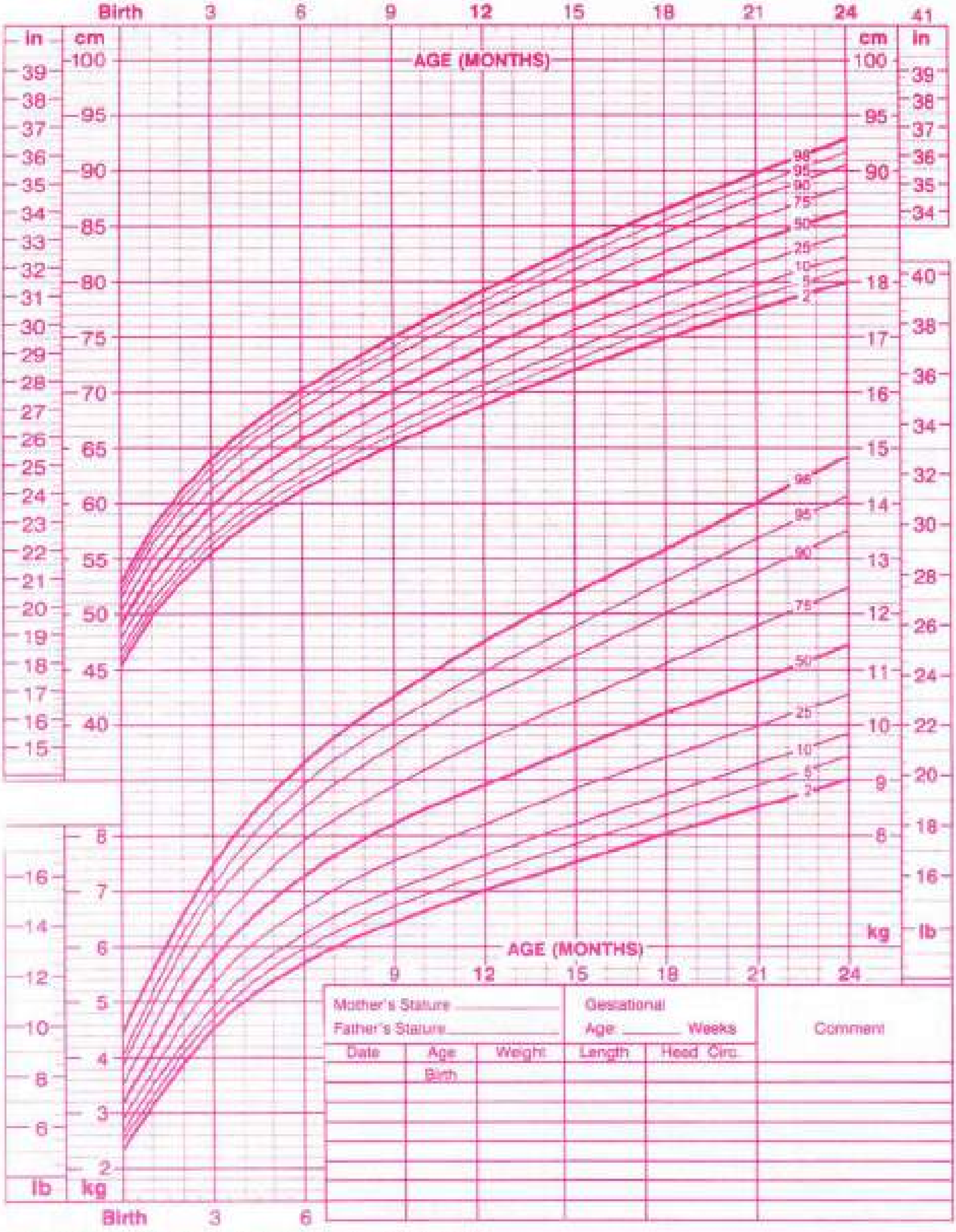
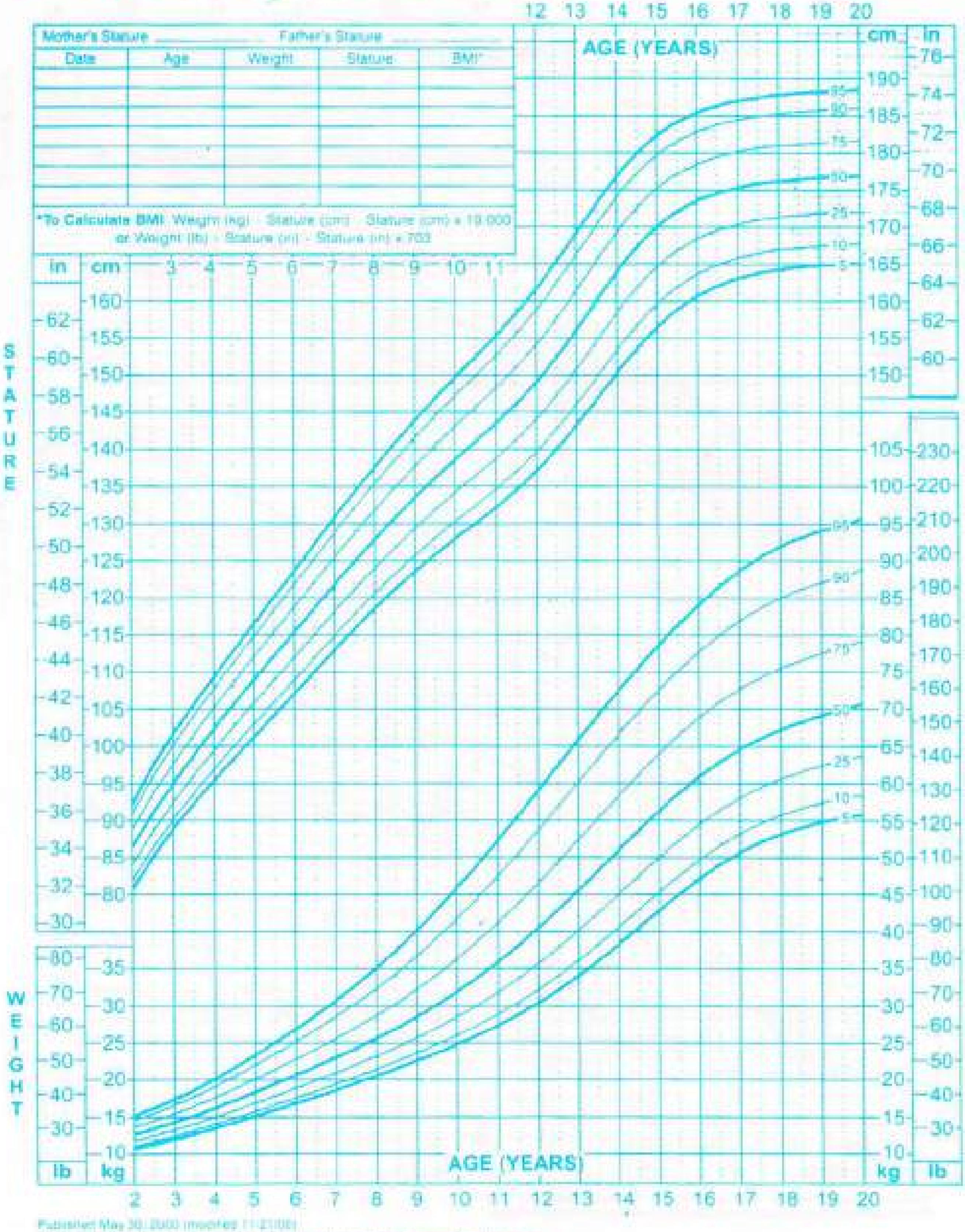


Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME ____________________

RECORD # ____________________



Mother's Stature ____________________ Father's Stature ____________________

Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) × 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) × 703

Published May 30, 2000 (modified 11/21/00)
SOURCE: Developed by the National Center for Health Statistics in collaboration with
the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

NAME ______________________

RECORD # ______________

Mother's Stature ______________ Father's Stature ______________

Date	Age	Weight	Stature	BMI*

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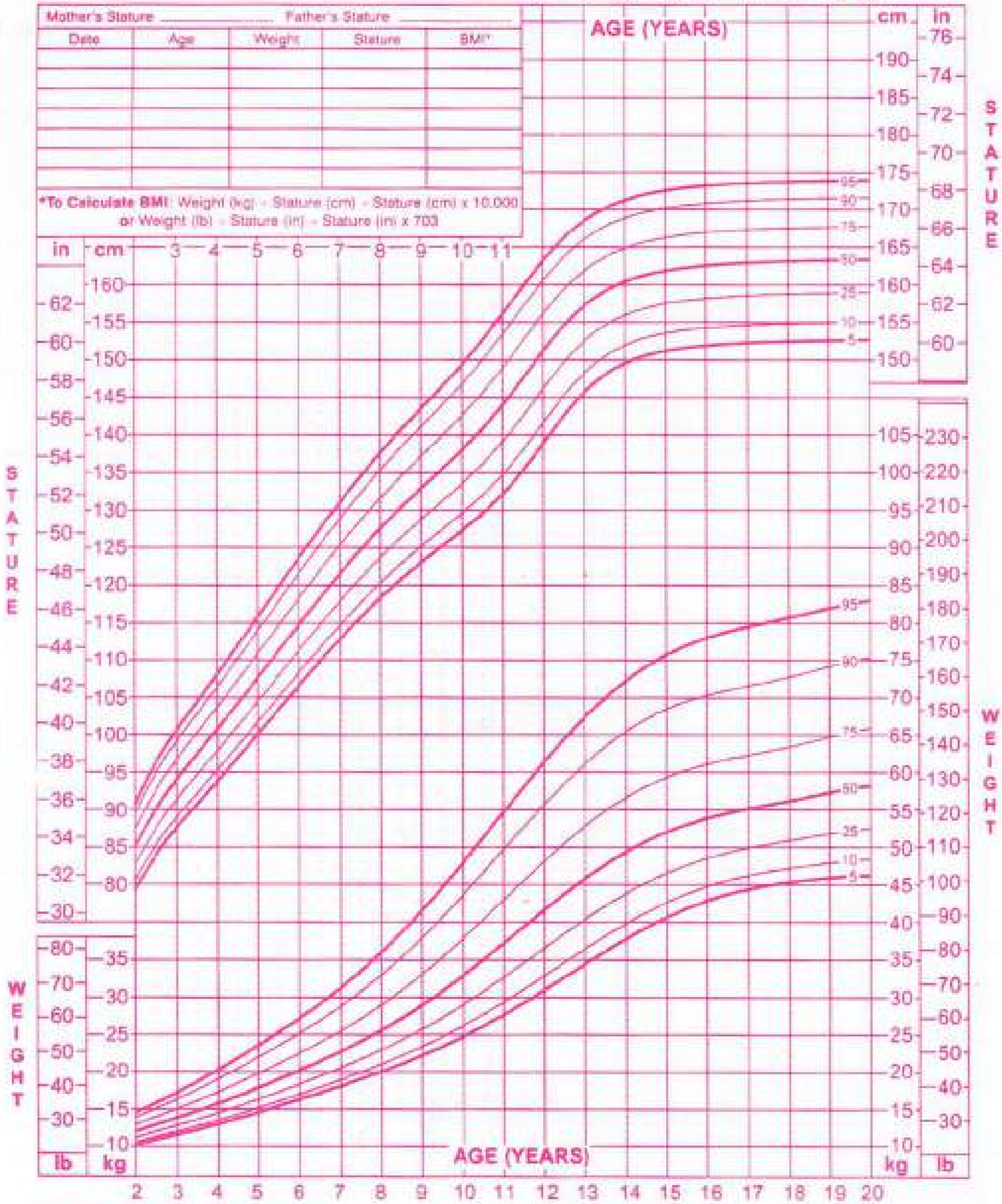
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



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http://www.cdc.gov/growthcharts

2 to 20 years: Boys
Body mass index-for-age percentiles

NAME ____________________

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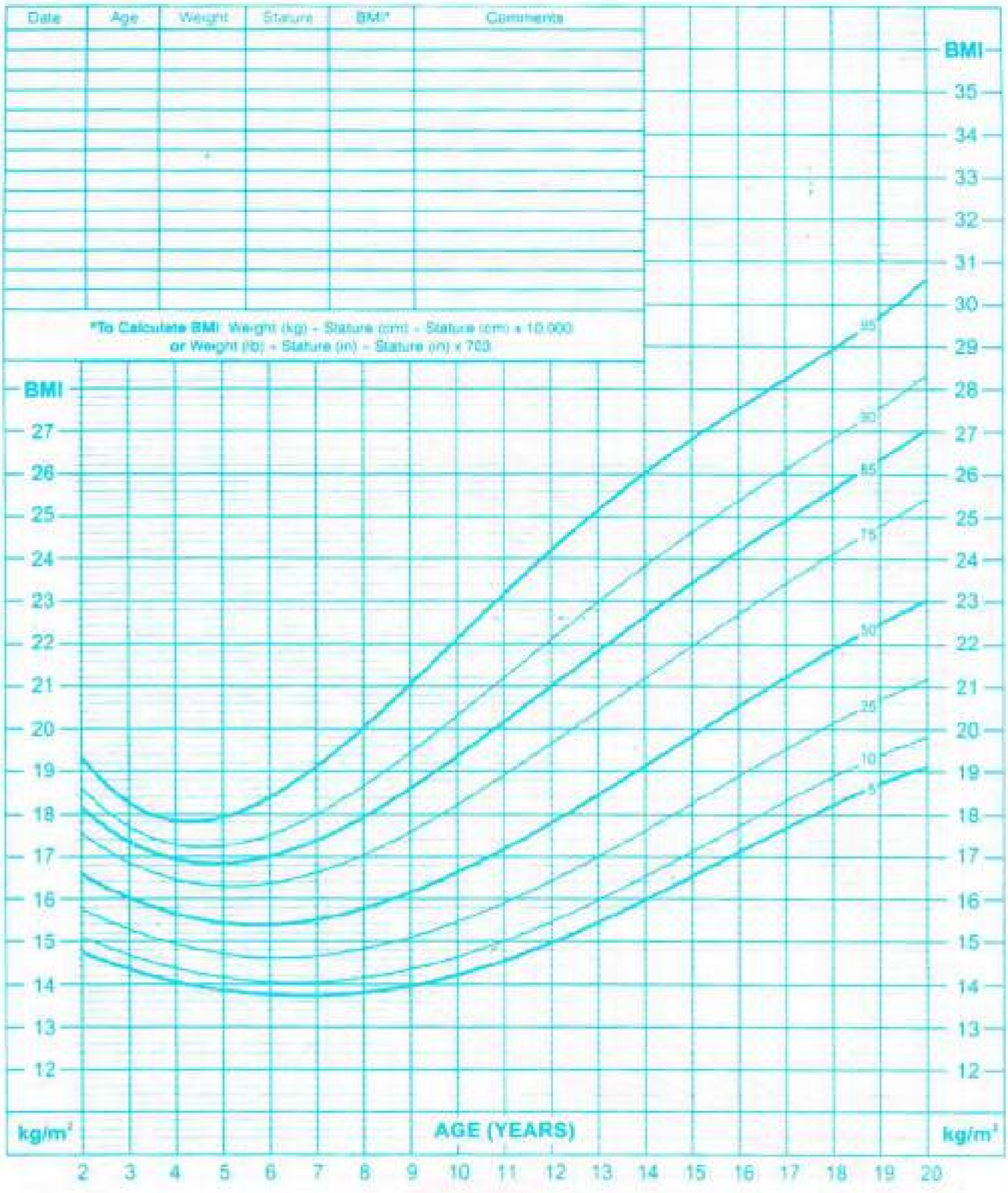

Date	Age	Weight	Stature	BMI*	Comments

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or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703

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2 to 20 years: Girls
Body mass index-for-age percentiles

NAME ______________________

RECORD # ______________

Date	Age	Weight	Stature	BMI*	Comments

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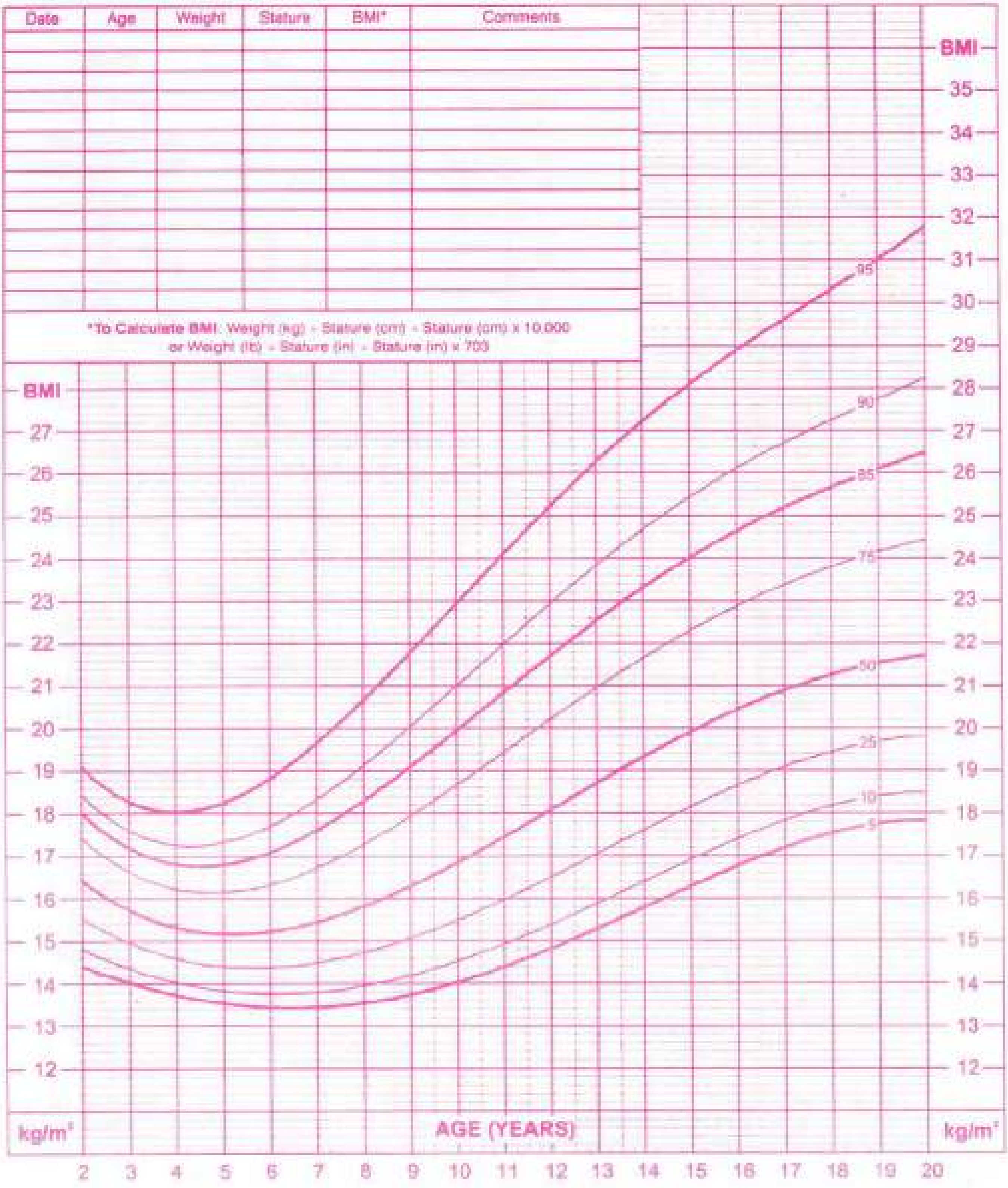
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



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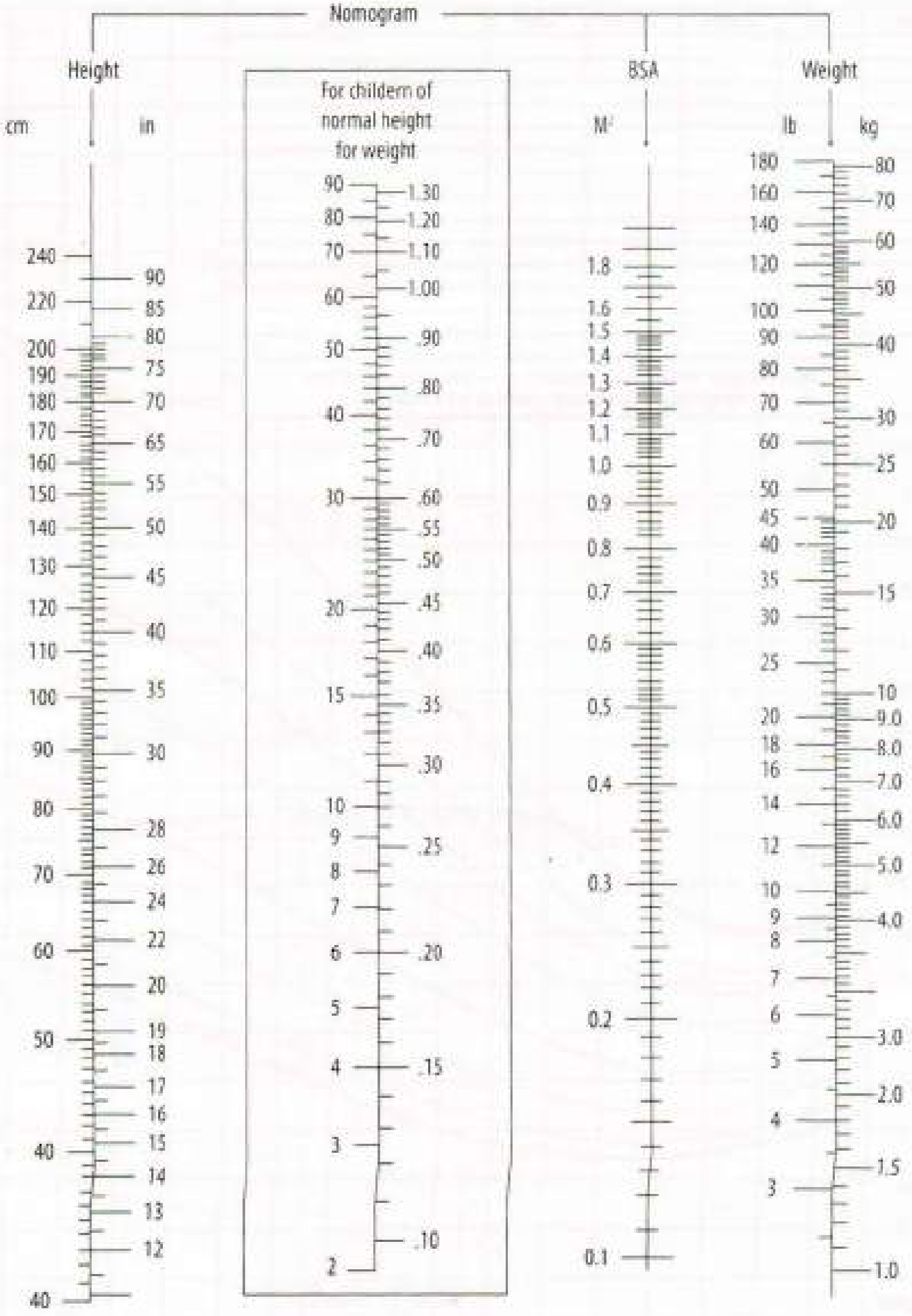
http://www.cdc.gov/growthcharts

SURFACE AREA MEASUREMENT



CHAPTER 03

Immunization

Definition

- Immunization is the process of inducing immunity against a specific disease.
- Immunity can be induced either passively through administration of antibody-containing preparations (immunoglobulins) or actively by administering a vaccine or toxoid.

Herd immunity

- Herd immunity exists if the number of people in a community who have active immunity against an infection exceeds a critical level.
- If this level is achieved then even non-vaccinated individuals are protected from getting the disease.

VACCINE

- The vaccine is usually a protein similar to part of a virulent infectious organism that can be recognized by the individual's immune system, which then produces antibodies or cell-mediated immunity against the antigen in the vaccine.
- Vaccines may be live, killed, toxoids, or genetically engineered.

Live attenuated vaccine

- A virulent organism is weakened so that it produces an antigenic response without the serious consequences of a wild organism infection.

Killed, or inactivated vaccine

- Killed or inactivated vaccine is prepared from virulent organisms or preformed antigen inactivated by heat, phenol, formaldehyde or some other means.

Conjugated vaccines

- The response to polysaccharide vaccine is incomplete and unreliable and consequently these have sometimes been conjugated with other antigens in an attempt to improve the immunological response.

Toxoid

- These are toxins, which have been rendered non-toxic by treatment with formaldehyde, but their antigenicity is maintained.
- Examples are:
  - Diphtheria toxoid
  - Tetanus toxoid

Examples of different vaccines

- **Live vaccines:**
  - BCG
  - Polio drops (OPV)
  - Measles
  - MMR
  - Rota virus
  - Varicella
  - Typhoid (oral)
  - Yellow fever
- **Killed/inactivated vaccines:**
  - Pertussis
  - Hepatitis A
  - Cholera
  - Influenza
  - Injectable polio (IVP)
  - Rabies
- **Toxoids:**
  - Diphtheria
  - Tetanus
- **Polysaccharide vaccines:**
  - Meningococcal
  - Pneumococcal
  - H. influenzae type b
  - Typhoid (IM)
- **Genetically engineered vaccines:**
  - Hepatitis B

IMMUNOGLOBULINS

- Passive immunity is achieved by administration of preformed antibodies (Immunoglobulins) to induce transient protection against an infectious agent.
- Passive immunity also can be induced naturally through transplacental transfer of maternal antibodies (IgG) during gestation. Maternally derived transplacental antibodies can provide protection during an infant's 1st month of life and longer during breastfeeding.

VACCINATION SCHEDULE

The following are the common infectious diseases against which World Health Organization (WHO) recommends routine immunization:

1. Tuberculosis
2. Diphtheria
3. Pertussis
4. Tetanus
5. Polio
6. Measles
7. Hepatitis B
8. H. influenzae type b
9. Pneumococcal pneumonia
   - The minimum interval between each dose of primary DPT and Polio vaccination should be 4

weeks. Even if months have elapsed between doses just complete the course
  - BCG is given intradermally in upper part of right deltoid
  - DPT is given intramuscularly in lateral side of right thigh at junction of upper 1/3 and lower 2/3
  - Hepatitis B vaccine is given intramuscularly in lateral side of left thigh at junction of upper 1/3 and lower 2/3
  - Measles vaccine is given subcutaneously in the middle of deltoid of left arm

Table 3.1: EPI (Expanded Program of Immunization) schedule by WHO in Pakistan.

	Age	Vaccine	Dose and route of administration
1st	Soon after birth	BCG	0.05 ml intra-dermal Rt deltoid
		OPV-0	2 drops
2nd	6 weeks	Pentavalent-1	0.5 ml IM
		OPV-1, Rota virus 1	2 drops
		Pneumococcal-1	0.5 ml IM
3rd	10 week	Pentavalent-2	0.5 ml IM
		OPV-2 Rota virus 1	2 drops
		Pneumococcal-2	0.5 ml IM
4th	14 weeks	Pentavalent-3	0.5 ml IM
		OPV-3	2 drops
		IPV	0.5 ml IM or SC
		Pneumococcal-3	0.5 ml IM
5th	After 9 months	Measles-1	0.5 ml SC
6th	After 15 months	Measles-2	0.5 ml SC

(Pentavalent vaccine contains a combination of diphtheria, pertussis, tetanus, hepatitis B and H. influenzae type b vaccine)

Table 3.2: In children who have not been vaccinated during infancy and are still below the age of 5 years vaccinate as follows:

BCG	Once on reporting
DT and Polio drops	2 doses at 6 weeks interval and 1st booster 6 months later
MMR	Once

PRECAUTIONS AND RECOMMENDATIONS

- Live vaccines should not be administered to children with immunodeficiency diseases.
- Injections should be given into the lateral thigh or into the deltoid.
- Deep injection and massage reduces the incidence of antigenic cysts.
- DPT injections may cause mild fever within 12–24 hours and it is not a contraindication for further immunization. Give paracetamol.
- If convulsions occur within 72 hours of DPT injection further administration of pertussis vaccine is contraindicated. Then give DT alone.
- After 2 years of age children should not receive pertussis vaccine.
- Children with brain damage or previous history of convulsions should not receive pertussis vaccine.
- In case of high risk due to contact with a case of pertussis, DPT can be initiated at 2 week of age.
- In the event of an epidemic or high risk, measles vaccine can be given at 6 months age.
- Immunization should be delayed only in case of illness with high fever, so that any sign of the illness will not be attributed to the vaccination.
- Administration of live attenuated vaccines should be delayed for at least six weeks when a recent injection of polyvalent immune globulin has been given.

CONDITIONS, WHICH ARE NOT CONTRAINDICATED TO IMMUNIZATION

- Minor illnesses such as upper respiratory infections or diarrhea, with fever <38.5 °C
- Allergy, asthma, or other atopic manifestations, hay fever or 'snuffles'
- Prematurity, small for date infants
- Malnutrition

BCG VACCINE

- BacilleCalmette Guerin (BCG) is the most widely used vaccine in the world
- BCG is made of a live, weakened (attenuated) strain of mycobacterium bovis

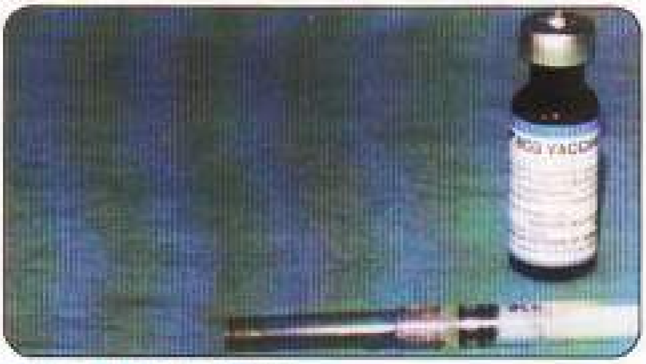


Figure 3.1: BCG vaccine vial.

- BCG vaccine has relatively high protective efficacy (approximately 80%) against meningeal and military tuberculosis in children. Protective efficacy against pulmonary tuberculosis is about 50%

Normal course of BCG

- The wheal of injection disappears in 30 minutes.
- Two to three weeks later a nodule forms which indurate and forms a superficial abscess. It ulcerates and heals in 4–6 weeks.
- The whole process is completed in 2 months and leaves a scar.

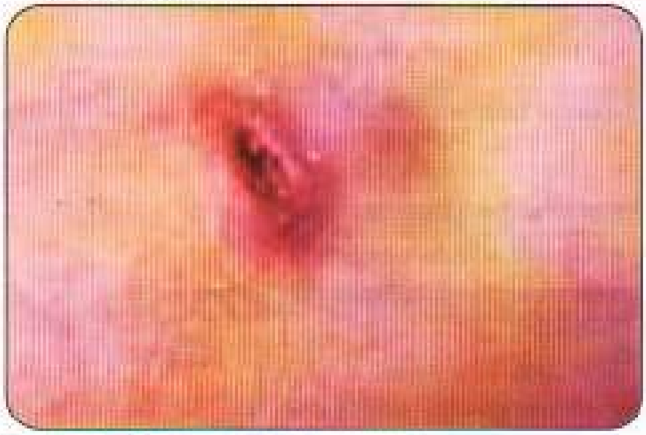


Figure 3.2: BCG vaccination ulceration.

Complications of BCG

- Koch's phenomenon i.e. accelerated reaction which completes in about 10 days.
- Deep abscess and ulceration.
- Lymphadenopathy of axillary nodes.

POLIOMYELITIS VACCINE

- Vaccines available against poliomyelitis are:
    - Live attenuated oral poliovirus vaccine (OPV, Sabin)
    - Injectable poliovirus vaccine (IPV, Salk)
- OPV contains live attenuated poliovirus type 1, 2 and 3.
- IPV also contains antigens of types 1, 2, and 3 polio virus.
- IPV is incapable of causing poliomyelitis by virtue of being inactivated, whereas OPV can do so rarely (risk of paralytic poliomyelitis with OPV is 1 in 6 million doses).
- Even if a child has suffered from poliomyelitis, he should be vaccinated so as to protect him against other two types of polioviruses.

Efficacy of vaccine

- >90% in industrialized countries
- 72–98% in hot climates
- Lower protection against type 3

Figure 3.3: Poliomyelitis vaccine.

Duration of immunity

- Lifelong if boosted by wild virus
- Factors that reduce the immune response in developing countries are:
    - Loss of cold chain
    - Interference from other enteroviruses

Advantages of OPV vaccine

- It is easy to administer
- It has superior antibody response
- Provides rapid immunity within 1 week
- Also provides herd immunity

Side effects of OPV

- Paralytic polio in immunized child (1:6 million)
- Paralytic polio in close contact of child immunized (1: 5 million)

Contraindications of OPV

- Infection with HIV or a household contact with HIV
- Known immunodeficiency (hematologic and solid tumors; congenital immunodeficiency, and long-term immunosuppressive therapy)
- Immune-deficient household contact

OPV not contraindicated

- Breastfeeding
- Current antimicrobial therapy
- Mild diarrhea

IPV in Pakistan

- The IPV will be given as a single dose with Pentavalent-3, OPV-3 and PCV-3 to children of 14 weeks of age.
- IPV is administered in a dose of 0.5 ml intramuscularly or subcutaneously.

DIPHTHERIA, TETANUS, and PERTUSSIS (DTaP) VACCINE

- Diphtheria, tetanus, and pertussis vaccines (DTP vaccines) have been given together in a combined vaccine and have led to dramatic reductions in each of these diseases.

- The clinical efficacy of diphtheria vaccine is not precisely known but has been estimated to be greater than 95%.

Contraindications and precautions

- DTP vaccines should not be used in individuals who have had an anaphylactic-type reaction to a previous vaccine dose or to a vaccine component.
- DTP should not be given to children who developed encephalopathy not attributable to another identified cause within 7 days of a previous dose of DTP.
- DTP vaccination should also be delayed in individuals with progressive neurologic disorders, such as infantile spasms, uncontrolled epilepsy, or progressive encephalopathy, until their neurologic status is clarified and stabilized.
- Precautions to DTP vaccination include:
  - High fever (≥40.5°F)
  - Persistent inconsolable crying
  - Shock like state within 48 hours of a previous dose of DTP or DTaP; seizures within 3 days of a previous dose of DTP or DTaP
  - Guillain-Barre syndrome less than 6 weeks after a previous tetanus containing vaccine
  - Moderate or severe acute illness with or without a fever

Adverse effects

- Local reactions, fever, and other mild systemic effects
- Persistent inconsolable crying lasting 3 hours or more, and
- Hypotonic-hyporesponsive episodes
- Severe neurologic effects have not been associated with DTaP vaccinations (<1 per 3.5 million doses of DTaP)

Vaccines available

- DTaP contains tetanus toxoid, diphtheria toxoid, and acellular pertussis vaccine. This DTaP is licensed for ages 6 weeks through 6 years.

MEASLES, MUMPS, RUBELLA (MMR) VACCINE

- Minimum age is 12 months for routine MMR vaccination.

Rubella vaccine

- The use of rubella vaccine is to prevent the serious consequences of rubella infection during pregnancy: miscarriage, fetal demise, and congenital rubella syndrome.
- Susceptible pubertal girls and postpubertal women should also be immunized.

Contraindications: (MMR)

- Anaphylactic reactions to neomycin
- During pregnancy
- Known immunodeficiency and long-term immunosuppressive therapy
- Anaphylactic reaction to gelatin

MEASLES IMMUNIZATION

Active immunization

- Measles vaccines are live, attenuated virus preparations derived from various measles virus strains.

Vaccine efficacy

- >90% at 12 months of age
- >85% at 9 months of age
- Lower efficacy when maternal antibody present

Duration of immunity

- Lifelong if boosted by wild virus.
- Shorter when no wild virus circulating.

Dose of vaccine

- 0.5 ml subcutaneously

Adverse effects

- Mild febrile illness or morbiliform rash
- Febrile convulsions
- Encephalitis. (Incidence 1: 30,000 following vaccination)

HEPATITIS B VACCINE

- Routine vaccination is given to all infants, children, and adolescents.

Efficacy

- Hepatitis B vaccine is 85% effective in preventing perinatally acquired infection.
- 80–95% effective in preventing most postnatally acquired infections.

Dose

- Dose of vaccine is 0.5 ml if age is less than 18 years.
- Dose is 1 ml if age is more than 18 years. Hepatitis B vaccine should be given only in the deltoid muscle for adolescents and children and in the antero-lateral thigh muscle for infants and neonates.
- Schedule is 0, 1, and 6 months.

Infants born to HBsAg–positive mothers

- Infants born to HBsAg–positive mothers should receive 0.5 ml of hepatitis B immune globulin (HBIg) within 12 hours after birth, and hepatitis B vaccine at a separate site.
- The second dose of vaccine is recommended at age 1–2 months and the third dose at age 6 months.
- At 12–15 months of age, immunized infants should be tested for antibody to HBsAg (anti-HBs). If the anti-HBs is positive, vaccination has been effective. If negative, HBsAg should be tested for; if the result is positive,

immunization has failed and the infant is a chronic carrier. If both HBsAg and anti–HBs are negative, the series should be repeated at 0, 1, and 6 months followed by repeat anti–HBs testing 1 month after the third dose.

For infants born to mothers of unknown HBsAg status

- For infants born to mothers of unknown HBsAg status, the same schedule should be followed except that HBIG be withheld until the HBsAg status is known.
- If she is HBsAg-positive, HBIg should be initiated as soon as possible but within 7 days after birth.

Post-exposure prophylaxis

- Post-exposure prophylaxis is indicated in individuals with inadvertent percutaneous or permucosal exposure to HbsAg-positive blood or household exposure of an infant less than 12 months of age to a caregiver with acute hepatitis B.
- **Unvaccinated individuals** should receive HBIg (0.06 ml/kg–maximum 5 ml–within 24 hours (its value after 7 days is unknown) and the first dose of hepatitis B vaccine at a separate site within 7 days after exposure.
- **Previously vaccinated persons** should be retested for anti-HBs. If levels are adequate (>10 mIU/ml), no treatment is necessary. If levels are inadequate, a booster dose is required.
- **In individuals who cannot be tested**, a dose of HBIg should be given. A known non-responder should receive either two doses of HBIg (1 month apart) or one dose of HBIg and one of vaccine.
- If the patient becomes a chronic carrier, all household contacts should also receive vaccination.

MENINGOCOCCAL VACCINE

- This vaccine, protecting against meningococcal serogroups A, C, Y, and W-135.
- Infections with Neisseria meningitidis cause significant morbidity and mortality. Even with appropriate treatment, meningococcal disease has an estimated case-fatality rate of 10–14%, and up to 19% of survivors are left with serious disabilities, such as neurologic deficits, loss of limbs or limb function, or hearing loss.
- Five serogroups of meningococcus (A, B, C, W-135, and Y) cause the vast majority of disease worldwide.
- Intensive research efforts have been made to develop an effective vaccine against serogroup B, which causes more than 50% of cases among children younger than 1 year of age.
- A single dose of MCV is recommended for young adolescents (aged 11–12 years) and for adolescents entering high school (approximately 15 years of age). Meningococcal vaccination is also recommended for certain groups at increased risk of invasive meningococcal disease, including persons living in or traveling to countries with endemic or hyperendemic meningococcal disease, persons with complement deficiencies, persons with functional or anatomic asplenia.

Dosage and schedule of administration

- MCV is given as a single intramuscular dose of 0.5 ml.
- Protective antibody levels are typically achieved within 10 days of vaccination.
- Persons 2-55-year-old who received MPSV4* more than 3–5 years previously, and who remain at increased risk of meningococcal disease, should be considered for an additional dose of MCV4 vaccination, although data are limited about the need and effectiveness of revaccination.

Contraindications and precautions

- MCV is contraindicated in anyone with a known severe allergic reaction to any component of the vaccine.
- MCV4 vaccination is contraindicated with a prior history of Guillain-Barre syndrome.
- MCV can be given to individuals who are immunosuppressed.

HAEMOPHILUS INFLUENZAE TYPE B VACCINE

- *H. influenzae* type b (Hib) causes a wide spectrum of serious bacterial illnesses, particularly in young children, including meningitis, epiglottitis, pneumonia, septic arthritis, and cellulitis.
- Before the introduction of effective vaccines, Hib was the leading cause of invasive bacterial disease in children younger than 5 years of age.

Dosage and schedule of administration

- Hib vaccination is routinely recommended for all infants.
- The vaccine dose is 0.5 ml given intramuscularly.
- The recommended interval between doses in the primary series is 8 weeks, but a minimal interval of 4 weeks is permitted.
- For infants who missed the primary vaccination series, a catch-up schedule is used.
- Hib vaccine is not generally recommended for children 5 years of age or older.

Contraindications and precautions

- Hib vaccine should not be given to anyone who has had a severe allergic reaction to a prior vaccine dose or to any vaccine components.
- Hib vaccine should not be given to infants before 6 weeks of age, since they appeared to develop immune tolerance and did not mount appropriate immune responses to subsequent doses.

Adverse effects

- Adverse reactions following Hib vaccination are uncommon.

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* MENINGOCOCCAL Polyvallant VACCINE

- Between 5% and 30% of vaccine recipients experience swelling, redness, or pain at the vaccination site.
- Systemic reactions such as fever and irritability are rare.

PNEUMOCOCCAL VACCINE

- *Streptococcus pneumonia* is the most common cause of invasive bacterial infection in children, with most invasive disease occurring in children younger than age 2 years.
- Pneumococcal vaccine is a purified mixture of polysaccharides from 23 pneumococcal types (PPV 23).

Dosage and schedule of administration

- Universal immunization of all infants with pneumococcal vaccine is now recommended, with four doses given at 2, 4, 6, and 12–15 months of age. For 2–5 years of age single dose of 0.5 ml intramuscular is recommended.
- It is not recommended under 2 months and over 5 years of age.
- Children at high risk of invasive pneumococcal disease include those with chronic cardiovascular, pulmonary (including cystic fibrosis but not asthma), and liver diseases; and those with anatomic and functional asplenia (including sickle cell disease), nephrotic syndrome, chronic renal failure, diabetes mellitus, cerebrospinal fluid leak, or immunosuppression (including those with HIV infection, complement deficiencies, malignancies, prolonged use of steroids, and organ transplants).
- Penicillin prophylaxis of patients with sickle cell disease should be continued regardless of vaccination with PPV23.
- If splenectomy or immunosuppression can be anticipated, vaccination should be done at least 2 weeks beforehand.
- Revaccination with PPV23 may be considered after 3–5 years in children at high risk of fatal pneumococcal infection.

Contraindications and precautions

- For PPV23, vaccination is contraindicated in individuals who suffered a severe allergic reaction such as anaphylaxis after a previous vaccine dose or to a vaccine component.
- PPV23 vaccination should be deferred during moderate or severe acute illness, with or without fever.
- A history of invasive pneumococcal disease is not a contraindication to vaccination.

Adverse effects

- The most common adverse effects associated with PPV23 administration are fever, induration, and tenderness at the injection site.
- When it is given simultaneously with DTaP, no increase in febrile seizures has been seen when compared with administration of DTaP alone.

TYPHOID VACCINE

- Two vaccines against Salmonella entericatyphi, the bacterium that causes typhoid fever, are currently available.
- A live attenuated vaccine given orally (Ty21a, vivotis).
- An inactivated vaccine composed of purified capsular polysaccharide (ViCPS) given parenterally. *
- Both vaccines protect 50–80% of vaccine recipients.
- The oral vaccine is most commonly used because of its ease of administration.
- However, noncompliance with the oral vaccine dosing schedule occurs frequently, and correct usage should be stressed or the parenteral ViCPS vaccine used.

Vaccines available

- Parenteral ViCPS (TyphimVi) is for intramuscular use.
- Oral live attenuated Ty21a vaccine is supplied as enteric-coated capsules.

Dosage and schedule of administration

- ViCPS is administered as a single intramuscular dose (0.5 ml) in the deltoid muscle, with boosters needed every 3 years if exposure continues. It is approved for children aged 2 years and older.
- The dose of the oral preparation is one capsule every 2 days for a total of four capsules, taken 1 hour before meals. The capsules should be taken with cool liquids and should be kept refrigerated. All doses should be administered at least 1 week prior to potential exposure. A full course of four capsules is recommended every 5 years if exposure continues. This vaccine is not approved for children younger than age 6 years. As with all live attenuated vaccines, Ty21a should not be given to immunocompromised patients.

Adverse reactions

- Both the oral and parenteral vaccines are well tolerated, and adverse reactions are uncommon and usually self-limited.
- The oral vaccine may cause gastroenteritis-like illness, fatigue, and myalgia, whereas the parenteral vaccine may cause local and abdominal pain, dizziness, and pruritus.

CHOLERA VACCINE

- This vaccine provides only partial protection (50%) of short duration (3–6 months).
- The vaccine may be administered subcutaneously or intramuscularly. A primary series consists of two doses at least 1 week apart. Boosters may need to be given as frequently as every 6 months.

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* VI capsular polysaccharide vaccine or Typhim VI

- Dose:
  Children up to 12 years age: 2 doses of 0.25 ml.
  After 12 years of age: 2 doses of 0.5 ml.

HEPATITIS A VACCINE

- The most recent recommendation to reduce hepatitis A incidence is the routine administration of hepatitis A vaccine (HepA) to all children 12–23 months of age.
- In addition HepA vaccination is indicated for the following groups:
  - Travelers to countries with high rates of hepatitis A
  - Children with chronic hepatitis B or hepatitis C infections or other chronic liver disease
  - Children with clotting factor disorders
  - Persons with an occupational exposure to hepatitis A
- HepA vaccines are considered very safe; tens of millions of doses have been administered, and no serious adverse events have definitively been caused by the vaccine.
- Vaccine efficacy is 94–100% against clinical hepatitis A.

Dosage and schedule of administration

- Hepatitis A vaccine is available in two formulations.
- For individuals between the ages of 1 and 18 years, vaccine is administered intramuscularly in two doses of 0.5 ml, separated by 6–12 months. Then, booster 0.5 ml 6–12 months following initial dose.
- For persons older than 18 years, a higher dose of vaccine is recommended, also in two doses of 1 ml. then, booster dose of 1 ml 6–12 months following initial dose.
- HepA vaccine is given intramuscularly, and may be given simultaneously with other vaccines, including HepB.

ROTAVIRUS VACCINE

- Rotavirus is the leading cause of hospitalization and death from acute gastroenteritis in young children worldwide.
- Vaccine is recommended to all infants at 2, 4, and 6 months of age.
- The vaccine is highly effective, with the three-dose series demonstrating 98% efficacy at preventing severe rotavirus gastroenteritis and 74% at preventing any rotavirus gastroenteritis.

Dosage and schedule of administration

- Rotavirus vaccine is a liquid vaccine given by mouth and should never be given by any other route of administration. Infants readily swallow the vaccine in most circumstances; however, if an infant spits up or vomits after a dose is administered, the dose should not be readministered; the infant can receive the remaining doses at the normal intervals.
- Infants should be given rotavirus vaccine 2 doses separated by an interval of at least 4 weeks. The first dose should be given at 6 weeks of age; subsequent dose should be given 4 weeks after the preceding dose and prior to 24 weeks of age.
- The vaccination schedule for rotavirus vaccine is more restrictive. Risk of intussusception following vaccination increases with increasing age.

Contraindications and precautions

- Rotavirus vaccine should not be given to infants with a severe hypersensitivity to any components of the vaccine, or to infants who had a serious allergic reaction to a previous dose of the vaccine.

INFLUENZA VACCINE

- Annual influenza vaccination is indicated for all children older than 6 months of age who have a chronic health condition that increases their risk of complications from influenza infection. Annual vaccination is now routinely recommended for all children aged 6–59 months. Members (including other children) of households with persons in high-risk groups and with children younger than age 5 years should also be immunized.

Dosage and schedule of administration

- Children younger than age 6 months should not be immunized.
- Two doses are recommended for children younger than age 9 years who are receiving influenza vaccine for the first time; subsequent seasons require single doses.
- Older children receiving vaccine for the first time require only a single dose.
- The dose for children aged 6–35 months is 0.25 ml given intramuscularly; for older children the dose is 0.5 ml given intramuscularly.
- The recommended site of vaccination is the anterolateral aspect of the thigh for younger children and the deltoid for older children.

VARICELLA VACCINE

- Vaccination prevents severe complications of varicella such as secondary bacterial infections, pneumonia, encephalitis, hepatitis, and reye syndrome.
- The vaccine has been shown to be more than 95% effective at preventing severe disease.

Dosage and schedule of administration

- Two doses (0.5 ml) of varicella (varilrix) vaccine are recommended for immunization of all healthy children aged 12 months and older.

- For children aged 12 months to 12 years the immunization interval is 3 months.
- For persons 13 years or older it is 4 weeks.
- Varicella vaccine may be given simultaneously with MMR at separate sites. If not given simultaneously, the interval between administration of VAR and MMR must be greater than 28 days.
- Varicella vaccine should be delayed 5 months after receiving intravenous immune globulin, blood or plasma.

Contraindications and precautions

- Contraindications to varicella vaccine vaccination include a severe allergic reaction after a previous vaccine dose or to a vaccine component.
- It is also contraindicated in children who have cellular immunodeficiencies.
- Varicella vaccine should not be given to pregnant women.

Adverse events

- The most commonly recognized adverse reactions, occurring in approximately 20% of vaccines, are minor injection site reactions.
- Additionally, 3–5% of patients will develop a rash at the injection site, and an additional 3–5% will develop a sparse varicelliform rash outside of the injection site.

Antibody preparations

- Varicella-zoster immune globulin (VZIg) is reliably used in high-risk susceptible persons who are exposed to VZV, such as :
    - Immunocompromised individuals without a history of chickenpox
    - Susceptible pregnant women
    - Newborns whose mothers develop varicella 5 days prior to delivery or within 48 hours after delivery
    - Hospitalized premature infants of 28 weeks' or more gestation (whose mother lacks a history of chickenpox or is seronegative)
    - Hospitalized premature infants less than 28 weeks' gestation (regardless of maternal history or serostatus)
- VZIg should be given as soon as possible after exposure, and should be administered within 96 hours.
- Newborns should be given one vial (125 U) intramuscularly.
- The dose for all others is 125 U/10 kg body weight intramuscularly (maximum dose, 625 U).

RABIES IMMUNIZATION

- Human rabies is preventable with appropriate and timely postexposure prophylaxis.
- Postexposure care consists of local wound care, passive immunization, and active immunization.
- Immediately after an animal bite, all wounds should be flushed and aggressively cleaned with soap and water. If possible, the wound should not be sutured.
- Passive immunization after high-risk exposure consists of the injection of human rabies immune globulin (RIg) near the wound.
- Active immunization is accomplished by completing a schedule of immunization with rabies vaccine.
- Rabies vaccines (lysovac) stimulate immunity after 7–10 days, and the immunity persists for 2 years or more postvaccination.

Dosage and schedule of administration

- 1 ml is given intramuscularly in the deltoid (for adults and older children) or anterolateral thigh (for infants and young children).

In previously unvaccinated individuals

- After proper wound care has been provided, an individual exposed to rabies should receive rabies vaccination and RIg.
- Vaccination is given on the day of exposure and on days 3, 7, 14, and 28 following exposure. RIg should also be given as soon as possible after exposure, ideally on the day of exposure, in a recommended dose of 20 IU/kg.
- If anatomically possible, the entire dose of RIg should be infiltrated into and around the wound. Any remaining RIg should be administered intramuscularly at an anatomic site distant from the location used for rabies vaccination.
- If RIg was not administered when vaccination was begun, it can be administered up to 7 days after the first dose of vaccine.

In previously vaccinated individuals

- RIg should not be administered, and only two doses of vaccine on days 0 and 3 after exposure are needed.

Adverse effects

- Approximately 30–74% of adults experience pain, swelling, induration, or erythema at the injection site; 5–25% may have mild systemic reactions such as headache, nausea, muscle aches, and dizziness.
- An immune complex–like reaction occurs in about 6% of persons 2–21 days after receiving booster doses of the rabies vaccine.

Notes

CHAPTER 04

Social and Preventive Pediatrics

PAKISTAN DEMOGRAPHIC & HEALTH SURVEY [illegible]

Table 4.1: Demographic indicators.

Population	207,774,520
Population under 15	38%
Population aged over 65	4%
Number of live births (thousands)	6047
Number of deaths (thousands)	1528
Birth registration coverage	42%
Gender distribution, newborn (ratio of male to female)	1.05
Total fertility rate (per woman)	3.6%
Crude birth rate	29%
Crude death rate	6.3%
Median (average) age (years)	23.6
Life expectancy (years)	66.5
Urban population	38%
World bank income classification	Lower middle

Table 4.2: Health indicators.

Neonatal mortality rate/1000 live births	42
Infant mortality rate/1000 live births	62
Under-5 mortality	74/1000
Maternal mortality rate	178/100,000
Deaths due to HIV/AIDS (per 100,000 population)	2.0
Deaths due to malaria (per 100,000 population)	1.1
Deaths due to tuberculosis among HIV-negative people (per 100,000 population	27
Newborns protected against tetanus (rank 85 in world)	69%
Immunization coverage	72%
(age 1-2 years) BCG DPT3 Polio 3 Hib 3 HepB3 Measles	 88% 75% 75% 75% 75% 73%
Diarrhea treatment with ORS	41%
Safe water access	95%
Adequate sanitation access	75%

Table 4.3: Nutritional indicators.

LBW births	22%
Early initiation of breastfeeding within first hour within twenty four hour	 19.6% 55.5%
Exclusive breastfeeding (<6 months)	48%
Start of weaning at 6-8 months	65%
Still breastfeeding at age 2 years	53%
Underweight (moderate and severe)	38%
Underweight (severe)	38%
Malnutrition prevalence	9.5%
Over weight children under 5	2.5%
Vitamin A supplementation full coverage	75%
Consumption of iodized salt	69.1%

Table 4.4: Utilization of health services (data refer to the latest year available from 2007).

Health Services	Percentage
Contraceptive prevalence	25
Antenatal care (4+ visits)	86
Births attended by skilled health personnel	86
Measles immunization (1 year olds)	61

Smear positive TB treatment–success	91
Hospital beds per 1000 people (2012) (rank 178 in world)	0.6

Table 4.5: Educational indicators.

Adult literacy rate	70% Male 60.4% Female
Primary school enrolment	69.1% Male 86.9% Female
Secondary school enrolment	37.7% Male 56.1% Female

CHILD RIGHTS

Child

- A child is defined as a person below the age of 18, unless the laws of a particular country set the legal age for adulthood younger.

Non-discrimination

- It applies to all children, whatever their race, religion or abilities; whatever they think or say, whatever type of family they come from.
- It doesn't matter where children live, what language they speak, what their parents do, whether they are boys or girls, what their culture is, whether they have a disability or whether they are rich or poor.
- No child should be treated unfairly on any basis.

Best interests of child

- The best interests of children must be the primary concern in making decisions that may affect them.
- All adults should do what is best for children.
- When adults make decisions, they should think about how their decisions will affect children.
- This particularly applies to budget, policy and law makers.

Protection of rights

- Governments have a responsibility to take all available measures to make sure children's rights are respected, protected and fulfilled.

Main features of child rights: (by UNICEF)

- Right of survival and development; children have the right to live
- Right to have a legally registered name and nationality
- Right to live with their parent (s), unless it is bad for them
- Right of privacy
- Right of protection from all types of violence
- Right of freedom of expression
- Right of freedom of thought
- Right of health and medical care
- Right of education
- Right of having a good standard of living
- Right of protection from child labor; the government should protect children from work that is dangerous or might harm their health or their education
- Right of protection from drug abuse
- Right of protection from sexual exploitation
- Right of special care and support for children with any kind of disabilities
- Right of leisure, recreation and cultural activities
- Right of administration of juvenile justice
- Right of refugee child; children have the right to special protection and help if they are refugees

CHILD ABUSE

CASE

Shaken baby syndrome: A 4-month-old infant presents with ***altered mental status changes***. On examination, he is sleepy and difficult to ***arouse***. There is swelling on his right arm. X-ray shows a ***bone fracture***. Anterior fontanel is bulging. Fundoscopic examination shows ***retinal hemorrhages***. Examination otherwise is unremarkable.

- **Definition:** Any act of commission or omission by individuals, institutions, or society as a whole, and any conditions resulting from such acts or inaction, which deprive children of equal rights and liberties, and/or interfere with their optimal development, constitute by definition, abusive or neglectful acts or conditions.
- The number of reports of child abuse or neglect has steadily increased internationally and nationally since mandated reporting to 'Children Protective Services' (CPS) and law enforcement agencies.
- Child abuse is seen in any part of society, but it is most common in under privileged, lower socio-economic class.
- Main risk factors are:
    - Parental separation
    - Poor parenting
    - Parental disharmony

Recognition of child abuse and neglect

History

Common features in history in child abuse cases are:

- Discrepant history
- Delay in seeking care
- Event or behavior by child that triggers a loss of control of parents
- History of abuse in the parent's childhood
- Inappropriate affect of the parents
- Pattern of increasing severity if no intervention

- Social or physical isolation of the child or parent
- Stress or crisis in the family or the parents
- Unrealistic expectations of parents for the child

Examination

Common features in physical examination are:

- Physical examination of a potentially abused child should be therapeutic and diagnostic.
- A complete head-to-toe examination is important because a history may be misleading and an unexpected illness may be detected.
- Documenting present and past growth parameters is an essential part of any pediatric examination. A static low weight for height may indicate chronic under-nutrition, a decline in the growth rate may signal the onset of a period of neglect.
- Lack of clean clothing and poor personal hygiene are signs of neglect.
- The child's behavior in the examination room can provide clues about abuse or neglect.
- The findings upon examination of physically abused children may include abrasions, alopecia, bites, bruises, burns, dental trauma, fractures, lacerations, ligature marks, or scars. Injuries may be in multiple stages of healing.
- In sexually abused children, genital and anal findings of injury are noted carefully.

Classification

There are different types of child abuse:

- Physical abuse
- Sexual abuse
- Emotional abuse

Physical abuse

- Physical abuse of children is the intentional, non-accidental use of physical force on the part of a parent or other caretaker interacting with a child in his care, aimed at hurting, injuring or destroying the child.
- If the child's history is incompatible with the child's injury, child abuse should be suspected and reported.
- It is also suspected in a child with multiple injuries or injuries in various stages of healing.
- The most common physical abuse injuries include multiple bruises, burns, abrasions, bites, black eye, subdural hematoma, and bone fractures.
- Physical abuse is most likely when a high-risk parent is responsible for the care of a high-risk child.
- **High risk parents** are parents with depression, low self-esteem, adverse social circumstances, domestic frictions, chronic ill-health, low income and unemployment, social stresses as housing crisis, intrafamilial conflicts with large families and parents who were themselves abused during their childhood.
- **High risk children** include children with chronic medical problems, premature babies, colicky babies, children with behavior problems, unwanted pregnancy, mentally or physically handicapped and children separated from mothers early in life.

Sexual abuse

- Sexual abuse involves a child in any act that is intended for the sexual gratification of an adult.
- The definition of sexual abuse includes:
    - Inappropriate exposure to sexual acts or materials
    - Passive use of children as sexual stimuli for adults (i.e. child pornography)
    - Actual sexual contact of children with adults
- A child's apparent consent to participate in sexual activity does not reduce the older person's responsibility or alter the diagnosis.

Emotional abuse

- Emotional abuse includes intentional, verbal or behavioral acts that result in adverse emotional consequences.
- Emotional neglect occurs when a caretaker intentionally does not provide nurturing, verbal, and behavioral actions that are necessary for healthy development.
- Emotional abuse includes rejection, isolation, criticism, or terrorizing of a child. Emotional abuse is usually difficult to document.

Causes of child abuse

- **Abuser's childhood**: Many abusive parents report having suffered what could be labeled emotional abuse during their own childhoods.
- **Family stresses and supports:** excessive stress on the parent or family causes a breakdown of inhibitions and a release of frustration on a child. Main stresses are death or serious illness of a friend or family member, serious financial difficulties, and conflicts in the workplace.
- **Socioeconomic status:** Lower job status and educational level may be associated with increased rates of child neglect and sexual abuse.
- **Maternal age:** Maternal age at the time of a child's birth appears to influence the likelihood of physical abuse but not of neglect. Mothers of abused children usually begin childbearing earlier than do non-abusing mothers.
- **Abusers as adults:** Although abusers as a group do not fall into any single psychiatric diagnosis, some patterns of mental illness have been associated with certain kinds of maltreatment.
- **Early parent-child interaction:** The period immediately after birth is a critical period for the formation of parent-child relationships. If a bond between the two fails to form at this time, the mother will not be motivated to adequately protect and nurture her child.
- **Characteristics of children at risk for abuse:** Increased rates of abuse have been reported among

handicapped children. Children who are socially, and emotionally isolated are at higher risk for sexual abuse.

Management

- Physical abuse injuries, sexually transmitted diseases, and medical sequelae of neglect should be treated immediately.
- Children with failure to thrive related to emotional and physical neglect need to be placed in a setting where they can be fed and cared for.
- Child in danger of recurrent abuse needs to be placed in a safe environment.
- If abuse or neglect is suspected, a report must be made to the local or state agency designated to investigate such matters.

CHILD NEGLECT

- Child neglect usually is defined as parental omissions in care that result in actual or potential harm to the child.
- Child neglect is the most common form of child maltreatment. The morbidity and mortality associated with neglect also are substantial.
- Physical problems include injuries, ingestions, inadequately treated illness, dental problems, malnutrition, and neurologic deficits.
- Psychosocial problems include difficulties with attachment in infancy, impaired cognitive development and learning difficulties, emotional and behavior problems, and delinquent and criminal behavior.
- Addressing child neglect falls well within the broad mission of pediatrics to protect children and enhance their health and well being.
- The following points pertain to the definition of neglect:
    - Both actual and potential harm are of concern: if harm seems unlikely, it probably is unwarranted to consider a given situation as neglect.
    - Both psychosocial and physical harm are of concern.
    - Both short-and long-term harm are of concern.
    - The adequacy of care exists on a continuum from excellent to very poor; different degrees of inadequacy require different responses.
    - Neglect usually involves a pattern (e.g. repeatedly missing school), although it can occur with single lapses in care (e.g. infant left alone in a bath).
    - The assessment of neglect must consider the cultural context in which children's needs are met (e.g. different ways of showing affection, caring).

Manifestations of possible neglect

- Noncompliance (non-adherence) with health-care recommendations
- Delay or failure in getting health care
- Hunger, failure to thrive, and unmanaged morbid obesity
- Drug-exposed newborns, older children
- Ingestions: injuries; exposure to second-hand smoke, guns, domestic violence; failure to use car seats/belts (may reflect inadequate protection from environmental hazards)
- Emotional (e.g. excessive quietness or apathy in a toddler), behavior (e.g. repetitive movements), and learning problems, especially if not being addressed; extreme risk-taking behavior (may reflect inadequate nurturance, affection, or supervision)
- Inadequate hygiene, perhaps contributing to medical problems
- Unmet educational needs
- Abandoned children
- Homelessness

Physical neglect

- Physical neglect may include the failure to provide basic food, shelter, and clothing.
- Children require adequate supervision for their safety and emotional well being. Preadolescent children are usually not suitable caretakers for their younger siblings.

Medical neglect

- Failure to obtain recommended preventive care, lack of compliance with prescribed treatment, or delay in seeking care for acute illnesses may constitute medical neglect.
- Failure to obtain prenatal care or the use of harmful drugs during pregnancy may also consider medical abuse or neglect.

Emotional neglect

- The most common feature of emotional neglect is the absence of normal parent-child attachment and a subsequent inability to recognize and respond to an infant's or child's needs.
- A common manifestation of emotional neglect in infancy is nutritional (non-organic) failure to thrive.

CHILD LABOR

- Child labor is a consequence of struggling for existence in the third world countries.
- Child is forced into premature adulthood to get the burden of a livelihood.
- Children are compelled to do the toughest jobs to get food.
- The adults do not fulfill Child rights.
- Child labor is the work, which involves some degree of exploitation, i.e. physical, mental and social.
- UNICEF has given a **comprehensive formulation to define child labor:**
    - Starting full time work at too early an age

  - Working too long within or outside the family so that children are unable to attend school
  - Work resulting in excessive physical, social and psychological strain upon the child
  - Work and life on the street in unhealthy and dangerous conditions
  - Inadequate remuneration for working outside the family
  - Too much responsibility at too early an age
  - Work that does not facilitate the psychological and social development of the child
  - Work that inhibits the child's self-esteem as in bonded labor and prostitution

Forms of child labor

There are many forms of child labor:

- Domestic house task: Cooking, child care, fetching water, cleaning utensils, washing clothes, etc. these are called invisible work
- Handicrafts and cottage industries: Weaving, leather work, woodwork, etc.
- Construction work
- Domestic service
- Mining
- Informal economy: Laundry, recycling rubbish
- Employed by others:
  - Bonded slaves
  - Skilled trades: Carpets, embroidery, gem polishing
- Industries/unskilled occupations
- Commercial: Shops, restaurants, hotels
- Begging
- Prostitution and pornography
- Self-employed: For e.g. shoe shining, car washing, and recycling rubbish, selling newspapers
- Agricultural child labor

Common problems due to child labor

- Habit disorders
- Personality disorders like irritability, temper tantrums, negativeness, fear, and inferiority complex
- Psychoneurotic disorders like nervousness, tremors, and headaches
- Antisocial behavior like stealing, sexual offences
- Drug abuse
- Different diseases, poor health
- Disabilities

Different steps that may lessen the disgrace of child

- To investigate the various aspects of the phenomenon of child labor
- Appropriate implementation and effective enforcement of legal measures
- Need for forming national commitment for designing effective poverty alleviation
- Primary and basic education needs to be expanded fast
- Measures for basic sanitary, health care and educational facilities
- To launch an effective campaign against child labor

IMCI
(Integrated Management of Childhood Illness)

- IMCI is a broad strategy to reduce childhood mortality and morbidity in developing countries. It includes interventions to:
  - Prevent illness
  - Reduce deaths from the most common child health problems
  - Promote child health and development
- IMCI program was launched in 1997.
- It was recognized that five conditions namely ARI (acute respiratory infection), diarrhea, measles, malaria, and malnutrition cause most of the deaths (7 out of 10) in children of developing countries.
- IMCI strategy is collaborated by the WHO and UNICEF. In this strategy, simple life-saving measures are used to reduce childhood mortality and morbidity by above-mentioned diseases.
- IMCI also has health promoting and preventive strategies such as:
  - Reducing missed opportunities for immunization
  - Breastfeeding
  - Nutritional counseling
  - Vitamin A and iron supplementation
  - Treatment of worm infestation
- The focus of the IMCI strategy is at 1st level health facilities to improve the quality of care of children less than 5 years of age.
- The program has three important qualities:
  - It deals with all the problems of the child simultaneously, because a child usually has more than one problem at a time.
  - No costly equipment is required for it's implementation such as stethoscope, microscope, X-ray, etc.
  - No technical expertise is required. Any health worker at 1st care level can implement the program.

Priority problems and practices affecting child

The IMCI strategy sets priorities to address the problems that have the greatest impact on child health.

- **Malnutrition** is associated with more than 50% of all childhood deaths. Although lack of family resources may be a factor, in most places malnutrition is caused by feeding practices that could be improved using existing sources. Improving breastfeeding alone could reduce the number of child deaths by more than 10%.
- **Feeding:** Improved complementary feeding could prevent more than 10% of deaths from diarrhea and acute respiratory infections, in particular pneumonia.

It could also reduce the prevalence of malnutrition by over 20%, and increase resistance to measles and other illnesses.

- **Vitamin A deficiency:** In areas of vitamin A deficiency, childhood mortality could be reduced by over 20% by improving the intake of vitamin A through diet or supplementation.
- **Measles:** Most of the 800,000 measles deaths each year could be prevented if all children receive measles immunization before the age of one year.
- Malaria causes over 600,000 child deaths every year. If children in malaria endemic areas slept under bed nets that have been treated with insecticide, child deaths due to malaria could be reduced by as much as 35%.
- **Acute Respiratory Infections (ARI)** cause over 2 million child deaths annually. Timely and appropriate care seeking, combined with adequate treatment, could reduce ARI mortality by over 20%.
- **Diarrhea:** Nearly all the 1.2 million child deaths each year caused by acute watery diarrhea could be prevented by corr,ect home care for diarrhea. This means giving increased fluids, continuing feeding, seeking appropriate medical attention when needed, and following treatment recommendations. Improved hygiene practices, including safe disposal of excreta and hand washing, can reduce the incidence of diarrhea by more than 10%.

The key family practices

Communities need to be strengthened and families supported to provide the necessary care to improve child survival, growth and development. The evidence suggests that families should:

- **Breastfeeding:** Breastfeed their infants exclusively for at least four months and, if possible, up to six months.
- **Weaning:** Starting at about six months of age, feed children freshly prepared energy and nutrient rich complementary food, while continuing to breast feed up to two years or longer.
- **Vitamin A:** Ensure that children receive adequate amounts of micronutrients (vitamin A and iron, in particular), either in their diet or through supplementation.
- **Cleanliness:** Dispose offfeces, including children's feces, safely; and wash hands after defecation, before preparing meals and before feeding children.
- **Vaccination:** Take children as scheduled to complete a full course of immunizations (BCG, DPT, OPV, and measles) before their first birthday.
- **Malaria:** Protect children in malaria-endemic areas, by ensuring that they sleep under insecticide-treated bed nets.
- **Development:** Promote mental and social development by responding to a child's needs for care, and through talking, playing, and providing a stimulating environment.
- **Fluids:** Continue to feed and offer more fluids, including breast milk, to children when they are sick.
- **Home treatment:** Give sick children appropriate home treatment for infections.
- **Referral:** Recognize when sick children need treatment outside the home and seek care from appropriate providers.
- **Follow-up:** Follow the health worker's advice about treatment, follow-up and referral.
- **Antenatal care:** Ensure that every pregnant woman has adequate antenatal care. This includes having at least four antenatal visits with an appropriate health care provider, and receiving the recommended doses of the tetanus toxoid vaccination. The mother also needs support from her family and community in seeking care at the time of delivery and during the postpartum and lactation period.

To provide this care, families need knowledge, skills, motivation and support. They need to know what to do in specific circumstances and as the child grows and develops.

IMCI case management process

The complete IMCI case management process involves the following:

- **Danger signs:** The health worker assesses a child by checking first for danger signs, asking questions about common conditions (cough or difficult breathing, diarrhea, fever, and ear problem), examining the child, and checking the nutrition and immunization status. The health worker also assesses the child for other health problems.
- **Classify illness:** The health worker classifies a child's illness using a colour-coded triage system. Because children often have more than one condition, the health worker classifies each illness according to whether it requires urgent pre-referral treatment and referral, specific medical treatment and advice, or simple advice on home management.
- **Treatment plan:** After classification, the health worker **identifies** specific treatments and develops an integrated treatment plan for each child. If a child requires urgent referral, the health worker gives essential treatment before the patient is transferred. If a child needs treatment at home, the health worker gives the first dose of drugs to the child.
- **Home management:** The health worker provides **practical treatment instructions**, including advising the caretaker on how to give oral drugs, how to feed and give fluids during illness, and how to treat local infections at home. The health worker asks the caretaker to return for follow-up on a certain date, and teaches them how to recognize signs that indicate the child should return immediately to the health facility.
- **Feeding management:** If the child is underweight, the health worker identifies treatment or refers the child, when appropriate. The health worker also provides **counseling** to solve feeding problems, including

assessment of breastfeeding practices. If a child should be immunized, the health worker gives immunizations.

- **Follow-up:** When the child is brought back to the clinic as requested, the health worker gives follow-up care and, if necessary, reassesses the child for new problems.

IMCI clinical guidelines are based on the following principles

- **Examining all sick children aged up to five years of age** for **general danger signs** and all young infants for signs of very severe disease. These signs indicate severe illness and the need for immediate referral or admission to hospital.
- The children and infants are then **assessed for main symptoms.** In older children the main symptoms include:
    - Cough or difficulty breathing
    - Diarrhea
    - Fever
    - Ear infection
- In young infants, the main symptoms include:
    - Local bacterial infection
    - Diarrhea
    - Jaundice
- Then in addition, all sick children are **routinely checked** for:
    - Nutritional and immunization status
    - HIV status in high HIV settings
    - Other potential problems
- Only a **limited number of clinical signs** are used, selected on the basis of their sensitivity and specificity to detect disease through classification.
- A combination of individual signs leads to a child's classification within one or more symptom groups rather than a diagnosis. The classification of illness is based on a color-coded triage system:
- "PINK" indicates urgent hospital referral or admission.
- "YELLOW" indicates initiation of specific outpatient treatment.
- "GREEN" indicates supportive home care.
- IMCI management procedures use a limited number of essential drugs and encourage active participation of caregivers in the treatment of their children.
- An essential component of IMCI is the counseling of caregivers regarding home care:
    - Appropriate feeding and fluids
    - When to return to the clinic immediately
    - When to return for follow-up

INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESS (IMCI)
ASSESS AND CLASSIFY THE SICK CHILD AGE 2 MONTHS UP TO 5 YEARS

ASSESS AND CLASSIFY THE SICK CHILD
ASK THE MOTHER WHAT THE CHILD'S PROBLEMS ARE

PNEUMONIA AND VERY SEVERE DISEASE

Check for general danger signs

Ask:	Look:
• Is the child able to drink or breastfeed? • Does the child vomit everything? • Has the child had convulsions?	• See if the child is lethargic or unconscious. • See if the child is convulsing now.

URGENT attention

Assess	Classify	Identify treatment
Any general danger sign.	Very severe disease	• Give diazepam if convulsing now. • Complete assessment quickly. • Give any pre-referral treatment immediately. • Keep the child warm. • Treat the child to prevent low blood sugar. • Refer urgently to hospital.

Then ask about main symptoms:
Does the child have cough or difficult breathing?

IF YES:
ASK: For how long?
LOOK, LISTEN: (child must be calm)

- Count the breaths in one minute. (If the child is 2 months up to 12 months, fast breathing is 50 breaths per minute or more; if the child is 12 months up to 5 years, fast breathing is 40 breaths per minute or more.)
- Look for chest indrawing.
- Look and listen for stridor.
- Look and listen for wheeze.

Classify cough or difficult breathing

• Any general danger sign or • Stridor in calm child or	Severe pneumonia or very severe disease	• **Give first dose of an appropriate antibiotic.** • **Refer urgently to hospital.**
Chest indrawing Fast breathing	Pneumonia	• Give oral amoxicillin for 5 days. • If wheezing (or disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days. • Soothe the throat and relieve the cough with a safe remedy. • If coughing for more than 14 days or recurrent wheeze, refer for possible TB or asthma assessment • Advise mother when to return immediately. • Follow-up in 3 days.
No signs of pneumonia or very severe disease	Cough or cold	• If wheezing (or disappeared after rapidly acting bronchodilator) give an inhaled bronchodilator for 5 days. • Soothe the throat and relieve the cough with a safe remedy. • If coughing for more than 14 days or recurrent wheezing, refer for possible TB or asthma assessment • Advise mother when to return immediately. • Follow-up in 5 days if not improving.

If pulse oximeter is available, determine oxygen saturation and refer if <90%.

DIARRHEA, DEHYDRATION, DYSENTERY

Does the child have diarrhea?		
IF YES: **ASK:** • For how long? • Is there blood in the stool?	**LOOK AND FEEL:** • Look at the child's general condition: Lethargic or unconscious? Restless and irritable? • Look for sunken eyes. • Offer the child fluid. Is the child: Not able to drink or drinking poorly? Drinking eagerly, thirsty? • Pinch the skin of the abdomen. Does it go back: Very slowly (longer than 2 seconds)? Slowly?	
CLASSIFY DIARRHEA		
For dehydration		
• At least two of the following signs: • Lethargic or unconscious • Sunken eyes • Not able to drink or drinking poorly • Skin pinch goes back very slowly	Severe dehydration	• If child has no other severe classification: • Give fluid for severe dehydration (plan C). OR • If child also has another severe classification: • Refer urgently to hospital with mother giving frequent sips of ORS on the way. Advise the mother to continue breastfeeding. • If child is 2 years or older and there is cholera in your area, give antibiotic for cholera.
• At least two of the following signs: • Restless, irritable • Sunken eyes • Drinks eagerly, thirsty • Skin pinch goes back slowly	Some dehydration	• Give fluid, zinc supplements, and food for some dehydration (plan B). • If child also has a severe classification: • Refer urgently to hospital with mother giving frequent sips of ORS on the ways. • Advise the mother to continue breastfeeding. • Advise mother when to return immediately. • Follow-up in 5 days if not improving.
• Not enough signs to classify as some or severe dehydration	No dehydration	• Give fluid, zinc supplements and food to treat diarrhea at home (plan A). • Advise mother when to return immediately. • Follow-up in 5 days if not improving.
If diarrhea 14 days or more		
• Dehydration present	Severe persistent diarrhea	• Treat dehydration before referral unless the child has another severe classification. • Refer to hospital.
• No dehydration	Persistent diarrhea	• Advise the mother on feeding a child who has persistent diarrhea. • Give multivitamins, minerals (including zinc supplement) for 14 days. • Advise mother when to return immediately. • Follow-up in 5 days.
and if blood in stool		
• Blood in stool	Dysentery	• Treat for 3 days with ciprofloxacin. • Advise mother when to return immediately. • Follow-up in 3 days.

SORE THROAT

Does the child have sore throat?

ASK:	LOOK and FEEL:
• Does the child have sore throat? • Is the child able to drink? • Does the child have fever?	• Fever (temperature 37.5°C or above). • Feel the front of the neck for tender enlarged lymph nodes. • Look for red, enlarged tonsils. • Look for exudate on the throat.

Classify sore throat

• Sore throat and not able to drink	Throat abscess	• Give first dose of appropriate antibiotic. • Treat the child to prevent low blood sugar. • Give first dose of paracetamol for high fever or pain. • Refer urgently to hospital.
• Fever and/or sore throat and at least two of the following signs • Tender, enlarged lymph nodes on neck • Red, enlarged tonsils	Streptococcal sore throat	• Give benzathinepencillin or amoxycillin. • Give paracetamol for high fever or pain. • Give safe, soothing remedy for sore throat. • Advise mother when to return immediately. • Follow-up in 5 days if not improving.
• Not enough signs to classify as throat abscess or streptococcal sore throat	Viral sore throat	• Give safe, soothing remedy for sore throat. • Give paracetamol for high fever or pain. • Advise mother when to return immediately. • Follow-up in 5 days if not improving.
• No signs present.	No throat problem	• No additional treatment.

EAR PROBLEM

Does the child have an ear problem?

ASK:	LOOK and FEEL:
• Is there ear pain? • Is there ear discharge? If yes, for how long?	• Look for pus draining from the ear. • Feel for tender swelling behind the ear.

Classify ear problem

• Tender swelling behind the ear	Mastoiditis	• Give first dose of an appropriate antibiotic. • Give first dose of paracetamol for high fever or pain. • Refer urgently to hospital.
• Pus is seen draining from the ear and/or discharge is reported for less than 14 days, OR • Ear pain	Acute ear infection	• Give an antibiotic for 5 days. • Give paracetamol for high fever or pain. • Dry the ear by wicking. • Advise mother when to return immediately. • Follow-up in 5 days.
• Discharge is reported for 14 or more days (pus is seen or not seen draining from the ear)	Chronic ear infection	• Dry the ear by wicking if pus seen draining from the ear. • Give paracetamol for high fever or pain. • Treat with topical quinolone eardrops for 14 days. • Follow-up in 5 days.
• No ear pain and no pus seen draining from the ear	No ear infection	• No treatment.

FEVER, MALARIA, MEASLES

Does the child have fever? (By history or feels hot or temperature 37.5°C or above)

IF YES: Decide Malaria Risk: high, low or no. If low or no malaria risk. Then ask: Has the child traveled to high or low malaria risk area in the last one month? Yes----------- No----------- (if yes, use the treatment instructions for the relevant malaria risk area) **THEN ASK:** • Fever for how long? • If more than 7 days, has fever been present every day? • Has the child had measles within the last 3 months?	**LOOK and FEEL:** • Look and feel for stiff neck. • Look for runny nose. Look for signs of measles. • Generalized rash of measles and • One of these: cough, runny nose, or red eyes. If the child has measles now or within the last 3 months: • Look for mouth ulcers. Are they deep and extensive? • Look for pus draining from the eye. • Look for clouding of the cornea.

Classify FEVER

High or Low Malaria Risk (high or low malaria risk area)

• Any general danger sign or • Stiff neck	Very severe febrile disease	• Give first dose of artesunate or quinine for severe malaria. • Give first dose of an appropriate antibiotic. • Treat the child to prevent low blood sugar. • Give one dose of paracetamol in clinic for high fever (38.5°C or above) • Refer urgently to hospital.
• Malaria test POSITIVE	Malaria	• Treat the child with recommended first line oral antimalarial. • Give one dose of paracetamol in clinic for high fever (38.5°C or above) • Advise mother when to return immediately. • Follow up in 3 days if fever persists. • If fever is present every day for more than 7 days, refer for assessment.
• Malaria test NEGATIVE • Other cause of fever PRESENT	Fever: No malaria	• Give one dose of paracetamol in clinic for high fever (38.5°C or above). • Give appropriate antibiotic treatment for an identified bacterial cause of fever. • Advise mother when to return immediately. • Follow-up in 3 days if fever persists. • If fever is present every day for more than 7 days, refer for assessment.

No malaria risk (no malaria risk area and no travel to malaria risk area)

• Any general danger sign or • Stiff neck	Very severe febrile disease	• Give first dose of an appropriate antibiotic. • Treat the child to prevent low blood sugar. • Give one dose of paracetamol in clinic for high fever (38.5°C or above) • Refer URGENTLY to hospital.
• *Fever and no travel to* malaria area	*Fever*	• Give one dose of paracetamol in clinic for high fever (38.5°C or above) • Treat other cause of fever *accordingly*. • Advise mother when to return immediately. • Follow up in 2 days if fever persists. • If fever is present every day for more than 7 days, refer for assessment.

If Measles now or within last 3 months, classify		
• Any general danger sign or • Clouding of cornea or • Deep or extensive mouth ulcers.	Severe complicated measles	• Give first dose of an appropriate antibiotic. • Give one dose of paracetamol in clinic for high fever (38.5°C or above) • If clouding of the cornea or pus draining from the eye, apply tetracycline eye ointment. • Give vitamin A treatment. • Refer urgently to hospital.
• Pus draining from the eye or • Mouth ulcers	Measles with eye and/or mouth complications	• Give one dose of paracetamol in clinic for high fever (38.5°C or above) • If pus draining from the eye, treat eye infection with tetracycline eye ointment. • Give vitamin A. • If mouth ulcers, treat with gention violet. • Advise mother when to return immediately. • Follow up in 3 days.
• Measles now or within the last 3 months	Measles	• Give one dose of paracetamol in clinic for high fever (38.5°C or above) • Give vitamin A. • Advise mother when to return immediately. • If measles now follow up in 2 days. • Follow up in 2 days if not improving.

MALNUTRITION

CHECK FOR ACUTE MALNUTRITION

LOOK AND FEEL:

- Look for signs of acute malnutrition.
- Look for edema of both feet.
- Determine WFH/L ___ z-score.
- Measure MUAC____ mm in a child 6 months or older.

If WFH/L less than-3 z-scores or MUAC less than 115 mm, then:

- **Check for any medical complication present:**
  - **Any general danger signs**
  - **Any severe classification**
  - **Pneumonia with chest indrawing**
- **If no medical complications present:**
  - **Child is 6 months or older, offer RUTF to eat. Is the child:**
    Not able to finish RUTF portion?
    Able to finish RUTF portion?
  - **Child is less than 6 months, assess breastfeeding:**
    Does the child have a breastfeeding problem?

Classify Nutritional Status		
• Edema of both feet **OR** • WFH/L less than-3 z-scores **OR** MUAC less than 115 mm **AND**any one of the following: ○ Medical complication present or ○ Not able to finish RUTF or ○ Breastfeeding problem.	Complicated severe acute malnutrition	• Give first dose appropriate antibiotic. • Treat the child to prevent low blood sugar. • Keep the child warm. • Refer urgently to hospital.

• WFH/L less than-3 z-scores **OR** • MUAC less than 115 mm **AND** • Able to finish RUTF	Uncomplicated severe acute malnutrition	• Give oral antibiotics for 5 days. • Give ready-to-use therapeutic food for a child aged 6 months or more. • Counsel the mother on how to feed the child. • Assess for possible TB infection. • Advise mother when to return immediately. • Follow up in 7 days
• WFH/L between-3 and-2 z-scores **OR** • MUAC 115 up to 125 mm	Moderate acute malnutrition	• Assess the child's feeding and counsel the mother on the feeding recommendations. • If feeding problem, follow up in 7 days. • Assess for possible TB infection. • Advise mother when to return immediately • Follow-up in 30 days
• WFH/L-2 z-scores or more **OR** • MUAC 125 mm or more	No acute malnutrition	• If child is less than 2-year-old, assess the child's feeding and counsel the mother on feeding according to the feeding recommendations. • If feeding problem, follow-up in 7 days.

- WFH/L is Weight-for-Height or Weight-for-Length determined by using the WHO growth standards charts.
- MUAC is Mid-Upper Arm Circumference measured using MUAC tape in all children 6 months or older.
- RUTF is Ready-to-Use Therapeutic Food for conducting the appetite test and feeding children with severe acute malnutrition.

ANEMIA

LOOK: Look for palmar pallor. Is it:
Severe palmar pallor?
Some palmar pallor?

Classify ANEMIA		
• Severe palmar pallor	Severe anemia	• Give iron. • Give mebendazole if child is 1 year or older and has not had a dose in the previous 6 months. • Advise mother when to return immediately. • Follow-up in 14 days.
• Some pallor	Anemia	• Give iron. • Give mebendazole if child is 1 year or older and has not had a dose in the previous 6 months. • Advise mother when to return immediately. • Follow-up in 14 days.
• No palmar pallor	No anemia	• If child is less than 2-year-old, assess the child's feeding and counsel the mother according to the feeding recommendations. • If feeding problem, follow-up in 5 days.

- Assess for sickle cell anemia if common in your area.
- If child has severe acute malnutrition and is receiving RUTF, DO NOT give iron because there is already adequate amount of iron in RUTF.

HIV INFECTION

ASK: Has the mother or child had an HIV test?
IF YES:
Decide HIV status:
- Mother: POSITIVE or NEGATIVE
- Child:
    - Virological test POSITIVE or NEGATIVE
    - Serological test POSITIVE or NEGATIVE

If mother is HIV positive and child is negative or unknown, ASK:

- Was the child breastfeeding at the time or 6 weeks before the test?
- Is the child breastfeeding now?
- If breastfeeding ASK: Is the mother and child on ARV prophylaxis?

If no, then test:

- Mother and child status unknown: TEST mother.
- Mother HIV positive and child status unknown: TEST child.

Classify HIV status		
• Positive virological test in child. OR • Positive serological test in a child 18 months or older.	Confirmed HIV infection	• Initiate ART treatment and HIV care. • Give cotrimoxazole prophylaxis. • Assess the child's feeding and provide appropriate counseling to the mother. • Advise the mother on home care. • Assess or refer for TB assessment and INH preventive therapy. • Follow-up regularly as per national guidelines.
• Mother HIV-positive AND negative virological test in a breastfeeding child or only stopped less than 6 weeks ago. OR • Mother HIV-positive, child not yet tested. OR • Positive serological test in a child less than 18 months old.	HIV exposed	• Give cotrimoxazole prophylaxis. • Start or continue ARV prophylaxis as recommended. • Do virological test to confirm HIV status. • Assess the child's feeding and provide appropriate counseling to the mother. • Advise the mother on home care. • Follow-up regularly as per national guidelines.
• Negative HIV test in mother or child.	HIV infection unlikely	• Treat, counsel and follow-up existing infections.

- Give cotrimoxazole prophylaxis to all HIV infected and HIV-exposed children until confirmed negative after cessation of breastfeeding.
- If virological test is negative, repeat test 6 weeks after the breastfeeding has stopped; if serological test is positive, do a virological test as soon as possible.

CHECK CHILD'S IMMUNIZATION, VITAMIN A AND DEWORMING STATUS

	Age	Vaccine
Immunization schedule	Birth	BCG*, OPV-0, HBV0
	6 weeks	DPT-1, OPV-1, HBV1, HIB1, RTV1,PCV1***
	10 weeks	DPT-2, OPV-2, HBV-2,HIB2, RTV2,PCV2
	14 weeks	DPT-3, OPV-3, HBV-3,HIB2, RTV3, PCV3
	9 months	Measles* *
	14 months	DPT

Vitamin A supplementation: Give every child a dose of Vitamin A every six months from the age of 6 months. Record the dose on the child's chart.

Routine worm treatment: Give every child mebendazole every 6 months from the age of one year. Record the dose on the child's card.

*Children who are HIV positive or unknown HIV status with symptoms consistent with HIV should not be vaccinated.

**Second dose of measles vaccine may be given at any opportunistic moment during periodic supplementary immunization activities as early as one month following the first dose.

***HIV-positive infants and pre-term neonates who have received 3 primary vaccine doses before 12 months of age may benefit from a booster dose in the second year of life.

FEEDING RECOMMENDATIONS DURING SICKNESS AND HEALTH

Feeding recommendations FOR ALL CHILDREN during sickness and health, and including HIV EXPOSED children on ARV prophylaxis

Newborn, birth up to 1 week	**1 week up to 6 months**	**6 up to 9 months**	**9 up to 12 months**	**12 months up to 2 years**	**2 years and older**
• Immediately after birth, put your baby in skin to skin contact with you. • Allow your baby to take the breast within the first hour. Give your baby colostrum, the first yellowish, thick milk. It protects the baby from many illnesses. • Breastfeed day and night, as often as your baby wants, at least 8 times in 24 hours. Frequent feeding produces more milk. • If your baby is small (low birth weight), feed at least every 2 to 3 hours. Wake the baby for feeding after 3 hours, if baby does not wake self. • DO NOT give other food or fluids. Breast milk is all your baby needs. This is especially important for infants of HIV positive mothers. Mixed feeding increases the risk of HIV mother-to-child transmission when compared to exclusive breastfeeding.	• Breastfeed as often as your child wants. Look for signs of hunger, such as beginning to fuss, sucking fingers, or moving lips. • Breastfeed day and night whenever your baby wants, at least 8 times in 24 hours. Frequent feeding produces more milk. • Do not give other food or fluids. Breast milk is all your baby needs.	• Breastfeed as often as your child wants. • Also give thick porridge or well mashed food, including animal source food and vitamin A-rich fruits and vegetables. • Start by giving 2 to 3 tablespoons of food. Gradually increase to ½ cups (1 cup = 250 ml). • Give 2 to 3 meals each day. • Offer 1 or 2 snacks each day between meals when the child seems hungry.	• Breastfeed as often as your child wants. • Also give a variety of mashed or finely chopped family food, including animal source food and vitamin A-rich fruits and vegetables. • Give 1/2 cup at each meal (1 cup = 250 ml). • Give 3 to 4 meals each day. • Offer 1 or 2 snacks between meals. The child will eat if hungry. • For snacks, give small chewable items that the child can hold. Let your child try to eat the snack, but provide help if needed. 	• Breastfeed as often as your child wants. • Also give a variety of mashed or finely chopped family food, including animal source food and vitamin A-rich fruits and vegetables. • Give 3/4 cup at each meal (1 cup = 250 ml). • Give 3 to 4 meals each day. • Offer 1 to 2 snacks between meals. • Continue to feed your child slowly, patiently. Encourage- but do not force-your child to eat. 	• Give a variety of family food to your child, including animal source food and vitamin A-rich fruits and vegetables. • Give at least 1 full cup (250 ml) at each meal. • Give 3 to 4 meals each day. • Offer 1 or 2 snacks between meals. • If your child refuses a new food, offer "tastes" several times. Show that you like the food. Be patient. • Talk with your child during a meal, and keep eye contact.

Wash your hands before preparing the child's food and use clean cooking utensils.

* A good daily diet should be adequate in quantity and include an energy-rich food (e.g. thick cereal with added oil/ghee/butter); meat, fish, eggs, or pulses; and fruits and vegetables.

Feeding recommendations for a child who has persistent diarrhea:

- If still breastfeeding, give more frequent, longer breastfeeds, day and night.
- If taking other milk:
  - Replace with increased breastfeeding or
  - Replace with fermented milk products, such as yogurt or
  - Replace half the milk with nutrient-rich semisolid food.
- For other food, follow feeding recommendations for the child's age.

TREAT THE CHILD

Teach the mother to give oral drugs at home

Follow the instructions below for every oral drug to be given at home.

Also follow the instructions listed with each drug's dosage table.

- Determine the appropriate drugs and dosage for the child's age or weight.
- Tell the mother the reason for giving the drug to the child.
- Demonstrate how to measure a dose.
- Watch the mother practice measuring a dose by herself.
- Ask the mother to give the first dose to her child.
- Explain carefully how to give the drug, then label and package the drug.
- If more than one drug will be given, collect, count and package each drug separately.
- Explain that all the oral drug tablets or syrups must be used to finish the course of treatment, even if the child gets better.
- Check the mother's understanding before she leaves the clinic.

Give an appropriate oral antibiotic

FOR PNEUMONIA, ACUTE EAR INFECTION

First line antibiotic is amoxicillin.

	Amoxicillin Give 2 times daily for 5 days	
Age or weight	**Tablet** 250 mg	**Syrup** 250 mg per 5 ml
2 months up to 12 months (4–<10 kg)	1	5 ml
12 months up to 3 years (10–<14 kg)	2	10 ml
3 years to 5 years (14–19 kg)	3	15 ml

- Amoxicillin is the recommended first-line drug of choice in the treatment of pneumonia due to its efficacy and increasing high resistance to cotrimoxazole.

FOR PROPHYLAXIS IN HIV CONFIRMED OR EXPOSED

Antibiotic for prophylaxis: Oral Cotrimoxazole

	Cotrimoxazole (trimethoprim + sulfamethoxazole) Give once a day starting at 4–6 weeks of age	
Age	**Syrup** (40/200 mg/5 ml)	**Pediatric tablet** (Single strength 20/100 mg)
Less than 6 months	2.5 ml	1
6 months up to 5 years	5 ml	2

FOR DYSENTERY

Give antibiotic recommended for 3 days. First line antibiotic is ciprofloxacin.

	Ciprofloxacine Give 15 mg/kg two times daily for 3 days	
Age	**Tablet** 250 mg	**Tablet** 500 mg
Less than 6 months.	½	¼
6 months up to 5 years	1	½

FOR CHOLERA

Give antibiotic recommended for cholera for 3 days.

Age or weight	**Erythromycin** (250 mg tablet) *Give four times daily for 3 days*	**Tetracycline** (250 mg tablet) *Give four times daily for 3 days*
2 years up to 5 years (10-19 kg)	1	1

Give an oral anti-malarial

Give Oral Antimalarial for malaria

- If Artemether-Lumefantrine (AL)
    - Give the first dose of artemether-lumefantrine in the clinic and observe for one hour. If the child vomits within an hour repeat the dose.
    - Give second dose at home after 8 hours.
    - Then twice daily for further two days as shown below.
    - Artemether-lumefantrine should be taken with food.
- If ArtesunateAmodiaquine (AS+AQ)
    - Give first dose in the clinic and observe for an hour, if a child vomits within an hour repeat the dose.
    - Then daily for two days as per table below using the fixed dose combination.

WEIGHT (age)	**Artemether-Lumefantrine tablets** (20 mg artemether and 120 mg lumefantrine) Give two times daily for 3 days			**Artesunate plus Amodiaquine tablets** Give Once a day for 3 days					
				(25 mg AS/67.5 mg AQ)			(50 mg AS/135 mg AQ)		
	Day 1	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**	**Day 1**	**Day 2**	**Day 3**
5-<10 kg (2 months up to 12 months)	1	1	1	1	1	1	-	-	-
10-<14 kg (12 months up to 3 years)	1	1	1	-	-	-	1	1	1
14-<19 kg (3 years up to 5 years)	2	2	2	-	-	-	1	1	1

Give paracetamol for high fever (≥38.5°C) or sore throat or ear pain

Give paracetamol every 6 hours until high fever or sore throat or ear pain is gone.

	Paracetamol	
Age or weight	**Tablet** (100 mg)	**Tablet** (500)
2 months up to 3 years (4–<14 kg)	1	¼
3 years up to 5 years (14–<19 kg)	1½	½

Give multivitamin/mineral supplement

Explain to the mother why the drug is given.

Determine the dose appropriate for the child's weight (or age)

Measure the dose accurately

Give vitamin A supplementation and treatment

VITAMIN A SUPPLEMENTATION

- Give first dose any time after 6 months of age to all children.
- Thereafter vitamin A **every six months**to all children.

VITAMIN A TREATMENT

- Give an extra dose of Vitamin A (same dose as for supplementation) for ***treatment*** if the child has MEASLES or persistent diarrhea. If the child has had a dose of vitamin A within the past month or is on RUTF for treatment of severe acute malnutrition, do not give Vitamin A.
- Always record the dose of Vitamin A given on the child's card.

Age	**Vitamin A dose**
6 months up to 12 months	100000 IU (Blue) capsule
One year and older	200000 IU (Red) capsule

Give Iron

Give one dose daily for 14 days.

Age or weight	**Iron/folate tablet** Ferrous sulfate 200 mg (60 mg elemental iron) + folate 250 mcg	**Iron syrup** Ferrous fumerate 100 mg/5 ml (20 mg elemental iron/ml)
2 months up to 4 months (4–6 kg)	-	1 ml (<¼ tsp)
4 months up to 12 months (6–10 kg)	-	1.25 ml (¼ tsp)
12 months up to 3 years (10–14 kg)	¼	2 ml (<½ tsp)
3 years up to 5 years (14–19 kg)	½	2.5 ml (½ tsp)

- Children with severe acute malnutrition who are receiving ready-to-use therapeutic food (RUTF) should not be given Iron.

TEACH THE MOTHER TO TREAT LOCAL INFECTIONS AT HOME

- Explain to the mother what the treatment is and why it should be given.
- Describe the treatment steps listed in the appropriate box.
- Watch the mother as she does the first treatment in the clinic (except for remedy for cough or sore throat).
- Tell her how often to do the treatment at home.
- If needed for treatment at home, give mother the tube of tetracycline ointment or a small bottle of gentian violet.
- Check the mother's understanding before she leaves the clinic.

Give mebendazole

- Give 500 mg mebendazole as a single dose in clinic if:
    - Hookworms/whipworms are a problem in children in your area
    - The child is 1 years of age or older
    - The child has not had a dose in the previous 6 months.

Treat eye infection with tetracycline eye ointment

- Clean both eyes 4 times daily.
    - Wash hands.

  - Use clean cloth and water to gently wipe away pus.
- Then apply tetracycline eye ointment in both eyes 4 times daily.
  - Squirt a small amount of ointment on the inside of the lower lid.
  - Wash hands again.
- Treat until redness is gone.
- Do not use other eye ointment or drops, or put anything else in the eye.
- Return to clinic immediately, if infection becomes worse.

Dry the ear by wicking and give ear drops

Dry the ear at least 3 times daily.

- Roll clean absorbent cloth or soft, strong tissue paper into a wick.
- Place the wick in the child's ear.
- Remove the wick when wet.
- Replace the wick with a clean one and repeat these steps until the ear is dry.
- Instill quinolone eardrops after dry wicking three times daily for two weeks.
  (Quinolone eardrops may include ciprofloxacin, norfloxacin, or ofloxacin)

Treat mouth ulcers with gentian violet (GV)

- Treat the mouth ulcers twice daily.
- Wash hands.
- Wash the child's mouth with clean soft cloth wrapped around the finger and wet with salt water.
- Paint the mouth with half-strength gentian violet (0.25%).
- Wash hands again.
- Continue using GV for 48 hours after the ulcers have been cured.
- Give paracetamol for pain relief.

Treat thrush with nystatin

- Treat thrush four times daily for 7 days.
- Wash hands.
- Wet a clean soft cloth with salt water and use it to child's mouth.
- Instillnystatin 1 ml four times a day.
- Avoid feeding for 20 minutes after medication.
- If breastfed check mother's breasts for thrush. If present treat with nystatin.
- Advise mother to wash breasts after feeds. If bottle fed, advise her to change cup and spoon.
- Give paracetamol if needed for pain.

Soothe the throat, relieve the cough with a safe remedy

- Safe remedies to recommend:
- Breast milk for exclusively breastfed infants.
- Honey with water; one-teaspoon honey in half cup of luke warm water.
- Green tea, soup, etc.
- Harmful remedies to discourage:
- Cough syrup containing codeine, antihistamines, alcohol, atropine, and expectorants.
- Oral and nasal decongestants.
- Do not massage or bind the chest.
- Do not give opium, alcohol.

Treat the convulsing child with diazepam

GIVE THESE TREATMENTS IN THE CLINIC ONLY

- Turn the child on the side to avoid aspiration.
- Do not insert anything in the mouth.
- Give 0.5 mg/kg diazepam injection solution per rectum using a small syringe without a needle (like a tuberculin syringe) or using a catheter.
- Check for low blood sugar, then treat or prevent.
- Give oxygen and refer.
- If convulsions have not stopped after 10 minutes repeat diazepam dose.

Age or weight	**DIAZEPAM** 10 mg/2 ml
2 months up to 6 months (5-7 kg)	0.5 ml
6 months up to 12months (7-<10 kg)	1.0 ml
12 months up to 3 years (10-<14 kg)	1.5 ml
3 years up to 5 years (14–19 kg)	2.0 ml

If high fever, lower the fever by sponging.

Give Artesunate suppositories or intramuscular artesunate or quinine for severe malaria

GIVE THESE TREATMENTS IN THE CLINIC ONLY
FOR CHILDREN BEING REFERRED WITH VERY SEVERE FEVER

- Check which pre-referral treatment is available in your clinic (rectal artesunate suppositories, artesunate injection or quinine).
- Artesunate suppository: Insert first dose of the suppository and refer child urgently.
- Intramuscular artesunate or quinine: Give first dose and refer child urgently to hospital.

IF REFERRAL IS NOT POSSIBLE

For artesunate injection

- Give first dose of artesunate intramuscular injection.
- Repeat dose after 12 hours and daily until the child can take orally.
- Give full dose of oral antimiarial as soon as the child is able to take orally.

For artesunate suppository

- Give first dose of suppository.
- Repeat the same dose of suppository every 24 hours until the child can take oral antimalarial.
- Give full dose of oral antimalarial as soon as the child is able to take orally.

For quinine

- Give first dose of intramuscular quinine.
- The child should remain lying down for one hour.
- Repeat the quinine injection at 4 and 8 hours later, and then every 12 hours until the child is able to take an oral antimalarial. Do not continue quinine injections for more than 1 week.

If low risk of malaria, do not give quinine to a child less than 4 months of age.

Age or weight	**Rectal artesunate suppository**		**Intramuscular artesunate**	**Intramuscular quinine**	
	50 mg suppositories Dosage 10 mg/kg	200 mg suppositories Dosage 10 mg/kg	60 mg vial (20 mg/ml) 2.4 mg/kg	150 mg/ml (in 2 ml ampoules)	300 mg/ml (in 2 ml ampoules)

2 months up to 4 months (4–6 kg)	1	-	½ ml	0.4 ml	0.2 ml
4 months up to 12 months (6–10 kg)	2	-	1 ml	0.6 ml	0.3 ml
12 months up to 2 years (10–12 kg)	2	-	1.5 ml	0.8 ml	0.4 ml
2 years up to 3 years (12–14 kg)	3	1	1.5 ml	1.0 ml	0.5 ml
3 years up to 5 years (14–19 kg)	3	1	2 ml	1.2 ml	0.6 ml

Give inhaled salbutamol for wheezing

USE OF A SPACER*

A spacer is a way of delivering the bronchodilator drugs effectively into the lungs. No child under 5 years should be given an inhaler without a spacer. A spacer works as well as a nebulizer if correctly used.

- From salbutamol metered dose inhaler (100 μg/puff) give 2 puffs.
- Repeat up to 3 times every 15 minutes before classifying pneumonia.

Spacers can be made in the following way

- Use a 500 ml drink bottle or similar.
- Cut a hole in the bottle base in the same shape as the mouthpiece of the inhaler.
- This can be done using a sharp knife.
- Cut the bottle between the upper quarter and the lower 3/4 and disregard the upper quarter of the bottle.
- Cut a small V in the border of the large open part of the bottle to fit to the child's nose and be used as a mask.
- Flame the edge of the cut bottle with a candle or a lighter to soften it.
- In a small baby, a mask can be made by making a similar hole in a plastic (not polystyrene) cup.
- Alternatively commercial spacers can be used if available.

To use an inhaler with a spacer

- Remove the inhaler cap. Shake the inhaler well.
- Insert mouthpiece of the inhaler through the hole in the bottle or plastic cup.
- The child should put the opening of the bottle into his mouth and breathe in and out through the mouth.
- A carer then presses down the inhaler and sprays into the bottle while the child continues to breath normally.
- Wait for three to four breaths and repeat.
- For younger children place the cup over the child's mouth and use as a spacer in the same way.

* If a spacer is being used for the first time, it should be primed by 4–5 extra puffs from the inhaler.

Treat the child to prevent low blood sugar

GIVE THE FOLLOWING TREATMENT

- **If the child is able to breastfeed:**
    - Ask the mother to breastfeed the child.
- **If the child is not able to breastfeed but is able to swallow:**
    - Give expressed breast milk or a breast-milk substitute.
    - If neither of these is available, give sugar water.
    - Give 30-50 ml of milk or sugar water before departure.
- **If the child is not able to swallow:**
    - Give 50 ml of milk or sugar water by nasogastric tube.
    - If no nasogastric tube available, give 1 teaspoon of sugar moistened with 1–2 drops of water sublingually and repeat doses every 20 minutes to prevent relapse.

* **To make sugar water:** Dissolve 4 level teaspoons of sugar (20 grams) in a 200–ml cup of clean water.

GIVE READY-TO-USE THERAPEUTIC FOOD

Give Ready-to-Use Therapeutic Food for Severe Acute Malnutrition

- Wash hands before giving the Ready-to-Use Therapeutic Food (RUTF).
- Sit with the child on the lap and gently offer the ready-to-use therapeutic food.
- Encourage the child to eat the RUTF without forced feeding.
- Give small, regular meals of RUTF and encourage the child to eat often 5–6 meals per day.
- If still breastfeeding, continue by offering breast milk first before every RUTF feed.
- Give only the RUTF for at least two weeks, if breastfeeding continue to breast and gradually introduce food recommended for the age (See Feeding recommendations in Counsel The Mother chart.
- When introducing recommended food, ensure that the child completes his daily ration of RUTF before giving other food.
- Offer plenty of clean water, to drink from a cup, when the child is eating the ready-to-use therapeutic food.

Recommended amounts of ready-to-use therapeutic food

CHILD'S WEIGHT (kg)	Packets per day (92 g Packets Containing 500 kcal)	Packets per Week Supply
4.0–4.9 kg	2.0	14
5.0–6.9 kg	2.5	18
7.0–8.4 kg	3.0	21
8.5–9.4 kg	3.5	25
9.5–10.4 kg	4.0	28
10.5–11.9 kg	4.5	32
>12.0 kg	5.0	35

Treat the diarrhea

See treatment plans in chapter of 'infectious diseases' under the heading of 'acute diarrhea'.

ASSESS, CLASSIFY AND TREAT THE SICK YOUNG INFANT AGE LESS THAN 2

DO A RAPID APRAISAL OF ALL WAITING INFANTS

ASK THE MOTHER WHAT THE YOUNG INFANT'S PROBLEMS ARE

- Determine if this is an initial or follow-up visit for this problem.
- If follow-up visit, use the follow-up instructions.
- If initial visit, assess the child as follows:

Check for possible infection

Ask:	Look, Listen, Feel:
• Has the young infant had convulsions (fits)? • Is the young infant vomiting everything? • Is the young infant not able to feed?	(Young infant must be calm) • See if the infant is convulsing now. • Count the breaths in one minute. Repeat the count if more than 60 per minute. • Look for severe chest indrawing. • Measure axillary temperature. • Look at the umbilicus. Is it red or draining pus? • Look for skin pustules. • Look at the young infant's movements. If infant is sleeping, ask the mother to wake him/her. ○ Does the infant move on his/her own? If the young infant is not moving, gently stimulate him/her. ○ Does the infant not move at all?

Classify all young infants		
Any one of the following signs • Not feeding well or • Convulsions or • Fast breathing (60 breaths per minute or more) or • Severe chest indrawing or • Fever (37.5 C) • Low body temperature (less than 35.5C) or • Movement only when stimulated or no movement at all.	Very severe disease	• Give first dose of intramuscular antibiotics. • Treat to prevent low blood sugar. • Refer urgently to hospital. • Advise mother how to keep the infant warm on the way to the hospital.
• Umbilicus red or draining pus. • Skin pustules.	Local bacterial infection	• Give an appropriate oral antibiotic. • Teach the mother to treat local infections at home. • Advise mother to give home care for the young infant. • Follow up in 2 days.
• None of the signs of very severe disease or local bacterial infection	Severe disease Or local Infection Unlikely	• Advise mother to give home care.

Then check for jaundice

If jaundice present, Ask:	**Look:**
• When did the jaundice appear first?	• Look for jaundice (yellow eyes or skin). • Look at the young infant's palms and soles. Are they yellow?

Classify jaundice		
• Any jaundice if age less than 24 hours. or • Yellow palms and soles at any age.	Severe jaundice	• Treat to prevent low blood sugar. • Advice the mother how to keep the young infant warm on the way to the hospital. • Refer urgently to hospital.
• Jaundice appearing after 24 hours of age. and • Palms and soles not yellow.	Jaundice	• Advise the mother to give home care for the young infant. • Advise mother to return immediately if palms and soles appear yellow. • If the young infant is older than 14 days, refer to a hospital for assessment. • Follow-up in 1 day.
• No jaundice present.	No jaundice	• Advise mother to give home care for young infant.

Then ask: does the young infant have diarrhea?

If yes, Ask:	**Look and Feel:**
• For how long? • Is there blood in the stool?	• Look at the young infant's general condition. Is the infant: ○ Does the infant move on his/her own? ○ Does the infant not move even when stimulated but then stops? ○ Does the infant not move at all? ○ Is the infant restless and irritable? • Look for sunken eyes. • Pinch the skin of the abdomen. Does it go back: ○ Very slowly (longer than 2 seconds). ○ Slowly?

Classify diarrhea

For dehydration

• At least two of the following signs: • Movement only when stimulated or no movement at all. • Sunken eyes. • Skin pinch goes back very slowly.	Severe dehydration	• If infant have no other severe classification: • Give fluid for severe dehydration (Plan C). or • If infant also has another severe classification: • Refer urgently to hospital with mother giving frequent sips of ORS on the way. • Advise mother to continue breastfeeding.
• At least two of the following signs: • Restless, irritable. • Sunken eyes. • Skin pinch goes back slowly.	Some dehydration	• Give fluid and food for some dehydration (Plan B). • If infant has any severe classification: • Refer urgently to hospital with mother giving frequent sips of ORS on the way. • Advise mother to continue breastfeeding. • Advise mother when to return immediately. • Follow-up in two days.
• Not enough signs to classify as some or severe dehydration.	No dehydration	• Give fluids to treat diarrhea at home (Plan A). • Advise mother when to return immediately. • Follow-up in two days.

Then check for feeding problem or low weight for age

Ask:	**Look, listen, feel:**
• Is the infant breastfed? If yes, how many times in 24 hours? • Does the infant usually receive any other food or drinks? If yes, how often? • If yes, what do you use to feed the infant?	• Determine weight for age. • Look for ulcers or white patches in the mouth (thrush).

Assess breastfeeding

- Has the infant breastfed in the previous hour?

  If the infant has not fed in the previous hour, ask the mother to put her infant to the breast. Observe the breastfeeding for 4 minutes (if the infant was fed during the last hour, ask the mother if she can wait and tell you when the infant is willing to feed again.)
- Is the infant well attached?

  Not well attached---------------Good attachment------------------

To check attachment, look for

- Chin touching breast.
- Mouth wide open.
- Lower lip turned outward.
- More areola visible above than below the mouth.

(all of these signs should be present if the attachment is good)

- Is the infant sucking effectively (that is, slow deep sucks, sometimes pausing)?

  Not sucking effectively---------Suckling effectively---------
- Clear a blocked nose if it interferes with breastfeeding.

Classify feeding

• Not well attached to breast or • Not suckling effectively or • Less than 8 breastfeeds in 24 hours or • Receives other food or drinks or • Low weight for age or • Thrush (ulcers or white patches in mouth).	Feeding problem Or Low weight	• If not well attached or not suckling effectively, teach correct positioning and attachment. ○ If not able to attach well immediately, teach the mother to express breast milk and feed by a cup. • If breastfeeding less than 8 times in 24 hours, advise to increase frequency of feeding. Advise the mother to breastfeed as often and as long as the infant wants, day and night. • If receiving other food or drinks, counsel the mother about breastfeeding more, reducing other food or drinks, and using a cup • If not breastfeeding at all: ○ Refer for breastfeeding counselling and possible relactation. ○ Advise about correctly preparing breast-milk substitutes and using a cup. • Advise the mother how to feed and keep the low weight infant warm at home. • If thrush, teach the mother to treat thrush at home • Advise mother to give home care for the young • Infant. • Follow-up any feeding problem or thrush in 2 days. • Follow-up low weight for age in 14 days.
• Not low weight for age or no other signs of inadequate feeding.	No feeding problem	• Advise mother to give home care for the young infant. • Praise the mother for feeding the infant well.

THEN CHECK FOR FEEDING PROBLEM OR LOW WEIGHT FOR AGE IN NON-BREASTFED INFANT

Ask

- What milk are you giving?
- How many times during the day and night?
- How much is given at each feed?
- How are you preparing the milk?
- Let mother demonstrate or explain how a feed is prepared, and how it is given to the infant.
- Are you giving any breast milk at all?

- What food and fluids in addition to replacement feeds is given?
- How is the milk being given?
- Cup or bottle?
- How are you cleaning the feeding utensils?

Look, Listen, Feel

- Determine weight for age.
- Look for ulcers or white patches in the mouth (thrush).

Classify feeding		
• Milk incorrectly or un-hygienically prepared or • Giving inappropriate replacement feeds or • Giving insufficient replacement feeds or • An HIV positive mother mixing breast and other feeds before 6 months or • Using a feeding bottle or • Low weight for age or • Thrush (ulcers or white patches in mouth).	Feeding problem Or Low weight	• Counsel about feeding. • Explain the guidelines for safe replacement feeding. • Identify concerns of mother and family about feeding. • If mother is using a bottle, teach cup feeding. • Advise the mother how to feed and keep the low weight infant warm at home. • If thrush, teach the mother to treat thrush at home. • Advise mother to give home care for the young infant. • Follow-up any feeding problem or thrush in 2 days. • Follow-up low weight for age in 14 days.
• Not low weight for age or no other signs of inadequate feeding.	No feeding problem	• Advise mother to give home care for the young infant. • Praise the mother for feeding the infant well.

CHAPTER 05

Behavioral and Psychiatric Disorders

PICA

CASE

A 2-year-child presents with anemia. He takes mainly milk in his diet and dislikes solid diet. There is also history of passing pin worms in stool. Mother tells that sometimes he eats dirt while playing.

- Pica is an eating disorder typically defined as the persistent eating of non-nutritive substances for a period of at least 1 month at an age in which this behavior is developmentally inappropriate (e.g. >18–24 months).
- Individuals presenting with pica have been reported to put in mouth and/or ingest a wide variety of non-food substances, including clay, dirt, sand, stones, pebbles, hair, feces, lead, soap, laundry starch, plastic, pencil erasers, fingernails, paper, paint chips, coal, chalk, wood, plaster, string, cigarette butts, ashes, wire, wool, and burnt matches.
- Pica may be a serious behavioral problem because it can result in significant medical sequelae.
- Pica has been shown to be a predisposing factor in accidental ingestion of poisons, particularly in lead poisoning or hyperkalemia following ingestion of burnt match heads.
- In particular, geophagia (soil or clay ingestion) has been associated with soil-borne parasitic infections, such as toxoplasmosis and toxocariasis.
- Although firm empirical data supporting any of the nutritional deficiency etiologic hypotheses are absent, deficiencies in iron, calcium, zinc, and other nutrients (e.g. thiamine, niacin, vitamins C and D) have been associated with pica.
- Maternal deprivation, parental separation, parental neglect, child abuse, and insufficient amounts of parent/child interactions have been associated with pica.
- The ingestion of paint is most common in children from low socioeconomic families and is associated with lack of parental supervision.
- Malnutrition and hunger also may result in pica.

Clinical findings

- The physical findings associated with pica are extremely variable and are related directly to the materials ingested and the subsequent medical consequences.
- Toxic ingestions: Lead toxicity is the most common. Physical manifestations of lead poisoning can include neurologic (e.g. irritability, lethargy, ataxia, incoordination, headache, cranial nerve paralysis, papilledema, encephalopathy, seizures, coma, death) and GI tract (e.g. constipation, abdominal pain, colic, vomiting, anorexia, diarrhea) symptoms.
- Infections and parasitic infestations: Toxocariasis and ascariasis are the most common soil-borne parasitic infections associated with pica.
- GI tract symptoms may be evident secondary to mechanical bowel problems, constipation, ulcerations, perforations, and intestinal obstructions caused by bezoar formation and the ingestion of undigestible materials into the intestinal tract.

Management

- Although pica in children often remits spontaneously, a multidisciplinary approach involving psychologists, social workers, and physicians is recommended for effective treatment.
- Combined behavioral, social, and medical approaches are generally indicated for pica.
- For co-occurring mental disorders and developmental delay, assessment for neglect and family supervision combined with a psychiatric assessment are important.
- The sequelae related to an ingested item can require specific treatment (e.g. lead toxicity, iron-deficiency anemia, parasitic infestation).
- Ingestion of hair can require medical or surgical intervention for a gastric bezoar.
- Removal of toxic substances from the environment, particularly lead-based paint, is important.
- Address any identified nutritional deficiencies; however, nutritional and dietary approaches have demonstrated success related to the prevention of pica in only a very limited number of patients.

NOCTURNAL ENURESIS

CASE

A 10-year-old boy presents with ***bedwetting***. There is no previous medical problem and no recent illness. He is

otherwise normal. Urinalysis and culture is ***negative***. He has an older sibling who was enuretic until the age of 12 years. Physical examination and blood pressure are normal. ***Urine specific gravity*** is 1.002 (normal 1.002–1.035).

Definition

- Voluntary or involuntary repeated discharge of urine into clothes or bed after a developmental age when bladder control should be established.

Etiology

- Delayed maturation of the cortical mechanisms that allows voluntary control of the micturition reflex
- Defective sleep arousal
- Reduced antidiuretic hormone production at night, resulting in an increased urine output (nocturnal polyuria)
- Genetic factors
- Bladder factors (lack of inhibition, reduced capacity, overactive)
- Constipation
- Organic factors, such as urinary tract infection or obstructive uropathy
- Sleep disorders e.g. adenoids

Main features

- By 5 yrs of age, 90–95% of children are nearly completely continent during the day, and 80–85% are continent at night.
- Nocturnal enuresis refers to the occurrence of involuntary voiding at night.
- Enuresis may be primary when nocturnal urinary control never achieved (estimated 75–90% of children with enuresis).
- Enuresis may be secondary when the child was dry at night for at least a few months and then enuresis developed (10–25% of children with enuresis).
- Approximately 60% of children with nocturnal enuresis are boys.
- Family history is positive in 50% of cases.

Clinical features and assessment

- A precise history includes: Family history of enuresis; pattern of enuresis (primary, secondary, nocturnal, diurnal); urinary frequency, urgency, dysuria, dribbling; history of constipation; and psychological stresses.
- Diabetes insipidus, diabetes mellitus, and chronic renal disease should be ruled out.
- Physical examination includes: height, weight, blood pressure, neurologic examination especially lower spinal vertebral function, examination of external genitalia for abnormalities e.g. hypospadias, and rectal examination for constipation.
- Urine examination should be done for specific gravity, glucose, protein, blood, and white blood cells. A urine culture should also be done.

Management

- The best approach to treatment is to reassure the child and parents that the condition is self-limited.
- Fluid intake should be restricted after 6 or 7 pm.
- The parents are advised to ascertain that the child voids at bedtime.
- Excessive sugar and caffeine after 4 pm are also avoided.
- If the child snores and the adenoids are enlarged, adenoidectomy can cure the enuresis.
- Active treatment should be avoided in children younger than 6 years of age, because enuresis is extremely common in younger children.

Behavioral approaches

- Counseling
- Charting
- Bladder stretching exercises
- Night awakening by parents 1 hour after sleep onset to void
- Use of a buzzer alarm when the child becomes wet

Pharmacologic management

- Desmopressin acetate (a synthetic analog of antidiuretic hormone) reduces urine production overnight. It is safe but has a high relapse rate on discontinuation. Dose is 0.2–0.6 mg at bedtime. Desmopressin acetate is effective in as many as 40% of children. It is used for 3–6 months when effective, and then tapered. If tapering results in recurrent enuresis, then higher doses are used.
- Anticholinergic therapyis indicated for therapy-resistant enuresis or children with symptoms of an overactive bladder. Oxybutynin 5 mg or tolterodine 2 mg at bedtime are used.
- A third-line treatment is imipramine (a tricyclic antidepressant). The dosage of imipramine is 25 mg in children age 6–8 years, and 50 mg in children age 9–12 years. Success rates are 30–60%. Side effects include anxiety, insomnia, and dry mouth, and heart rhythm may be affected.
- In unsuccessful cases, combining therapies often is effective.
- Alarm therapy plus desmopressin
- Combination of oxybutynin chloride and desmopressin
- Desmopressin and imipramine also may be combined

ENCOPRESIS

CASE

A 5-year-old girl presents with complaint of ***soiling***. Her ***parents had separated*** when she was 2-year-old. She was ***not toilet trained*** at that age. There is off and on history of ***constipation***.

Definition

- Fecal incontinence in a child age 4 years (or developmental equivalent) or older.
- Not due to medication or a medical disorder.

Main points

- **Functional encopresis** is defined as the repeated passage of feces in inappropriate places by a child of at least the developmental equivalent of age 4 years.
- In **retentive encopresis**, also called psychogenic megacolon, the child withholds bowel movements, leading to the development of constipation, fecal impaction, and the seepage of soft or liquid feces around the margins of the impaction into the underclothing.

Figure 5.1: A child with encopresis.

- Children with **continuous encopresis** have never gained primary control of bowel function.
- Children with **discontinuous encopresis** have a history of normal bowel control for an extended period. Loss of control often occurs in response to a stressful event, such as a separation or family illness.
- In the infrequent case of **toilet phobia**, a young child views the toilet as a frightening structure to be avoided.

Etiology

- Developmental and behavioral factors:
  - Lack of adequate school bathroom facilities
  - Harsh toilet training
  - Sexual abuse
  - Negative defecation experience (associated with prior diarrhea)
- Anatomical factors:
  - Hirschsprung's disease
  - Anal stenosis

Clinical assessment

- A detailed bowel history is needed:
  - Age of the child at toilet training.
  - Frequency of bowel movements.
  - History of constipation.
  - Description of the stools.
- Physical examination includes growth patterns assessment, neurologic examination evaluating lower limb deep tendon reflexes, abdominal examination, rectal examination (sphincter tone, presence of stool in the rectal ampulla).
- Thyroid testing.
- Abdominal radiograph to determine the extent of fecal retention.
- Anal manometery or rectal biopsy in case of Hirschsprung's disease.

Differential diagnosis

- Hirschsprung disease.
- Neurologic disorders.
- Hypothyroidism.
- Hypercalcemia.
- Anal fissures, which cause withholding of bowel movements.

Management

- Children with coexisting illnesses need to receive treatment for those conditions before focusing treatment on encopresis.
- With the most common type of encopresis, the retentive type, efforts are made to soften stool with enemas and laxatives so that constipation and painful defecation do not complicate the problem.
  - Enemas and laxatives or stool softeners will remove retained stool
  - Mineral oil (1–2 tablespoons twice daily with gradual discontinuation after 4–6 months)
  - Bowel retraining by sitting on the toilet after meals to take advantage of the gastrocolic reflex
  - Dietary changes with increased roughage and liquid and decreased milk and milk products
- In the case of continuous encopresis, the family is taught to train the child.
- For toilet phobia, a progressive series of rewarded desensitization steps is necessary.
- Children with discontinuous encopresis that persists over several weeks often need psychotherapy.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

CASE

A 7-year-old boy is always ***very active***. In school, he is disruptive. His teacher says that he is ***easily distracted*** and routinely fails to complete both homework classwork. At home he also has difficulty in completing tasks. Although the child is very talkative, he cannot answer questions clearly. He has normal hearing and no sign of neuro-developmental disorder.

Definition

- ADHD involves an inadequate attention span, impulsiveness, and hyperactivity. The syndrome in general is marked by a lack of task performance and easy distractibility.

Table 5.1: Main characteristics of ADHD.

- Short attention span
- Distractibility
- Poor impulse control
- Marked over activity

General considerations

- The prevalence of ADHD in children is 3–7%. ADHD is associated with significant psychiatric co-morbidity. Approximately 50–60% of individuals with this disorder may have coexisting conditions, which include learning disorders, restless-legs syndrome, ophthalmic convergence insufficiency, depression, anxiety disorder, anti-social personality disorder, substance abuse disorder, conduct disorder, and obsessive-compulsive behavior.

Table 5.2: Predisposing etiology of ADHD.

- Chronic disease
- Syndromes
- Mental retardation
- Acquired brain injury
- Psychosocial stresses
- Intolerant parents and caregivers
- Emerging conduct disorders

- ADHD is more frequently diagnosed in boys than in girls. Hyperactive symptoms may decrease with age because of developmental trends toward self-control. However, persons with ADHD developmentally mature later than the average population. Inattentive symptoms do not appear to have a similar developmental advantage and tend to remain constant into adulthood.

Pathophysiology

- Frontal cortex and the circuits linking them to the basal ganglia are critical for executive function and, therefore, to attention and exercise inhibition.
- Catecholamines are the main neurotransmitters with frontal-lobe function.
- Dopaminergic and noradrenergic neurotransmission appear to be the main targets for medications used to treat ADHD.
- Brains of children and adolescents with ADHD are 3–4% smaller than those of children without the disorder. The more severe ADHD symptoms, the smaller will be their frontal lobes, temporal gray matter, caudate nucleus, and cerebellum.

Clinical findings

Inattention

- Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through with instructions and does not finish schoolwork, chores, or duties in the workplace
- Often has a difficulty with organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in homework that requires sustained mental effort
- Often loses things necessary for tasks or activities (e.g. school assignments, pencils, books, tools, toys)
- Often is easily distracted by extraneous stimuli
- Often is forgetful in daily activities

Hyperactivity/Impulsivity

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs around or climbs excessively in situations in which this behavior is inappropriate
- Often has difficulty playing or engaging in leisure activities quietly
- Often on the go or often acts as if driven by a motor
- Often talks excessively
- Often blurts out answers to questions before questions are completed
- Often has difficulty waiting turns
- Often interrupts or intrudes on others (e.g. butts into conversations or games)

Diagnosis

- Liver function tests may be indicated if the patient has a history of hepatic dysfunction as many medications used in ADHD are metabolized in liver and excreted in urine.
- Determination of complete blood cell counts. A coincident relationship has been reported between use of methylphenidate and blood dyscrasias.
- Drug screening: Consider periodic random drug screening by means of urine testing or serum testing in all patients with a history of chemical abuse or suspected chemical abuse.
- Psychometric and educational testing is often important for the diagnosis of ADHD. Assess the patient's executive function by using various neuropsychologic tests. Several well-validated intelligence-quotient (IQ) tests are available.
- Baseline ECG to access the QT interval may be indicated before a tricyclic antidepressant is prescribed.

Management

- Behavior management:
  - Increasing structure in the environment
  - Positive reinforcement
  - Counseling
  - A number of cognitive approaches that emphasize relaxation and self-control
- Special education: Highly structured classrooms with low student-teacher ratios to emphasize their educational experiences.
- Medications:

Stimulants (methyl-phenidate)

Tricyclic antidepressants (imipramine)

AUTISM SPECTRUM DISORDER
(Pervasive developmental disorder)

CASE

A 5-year-old boy presents with complaint that he is not behaving properly. His ***speech is delayed***. He ***avoids contact with others***. He does not play with his siblings. On examination, he is avoiding contact but is cooperative and oriented. His gait, reflexes, and tone are normal. He is below 10th centile in height and weight.

- Autism is a neurologic disorder characterized by:
  - Qualitative impairments in social interaction
  - Qualitative impairments in communication
  - Restricted repetitive and stereotyped patterns of behavior, interests, and activities
- Autism spectrum disorders occur in approximately 1 in 150 children.
- No known etiology can be found in 80–90% of cases.
- A genetic syndrome such as fragile X syndrome is found in 10–20% of cases.
- There is a strong familial component. Parents of one child with autism of unknown etiology have a 2–9% chance of having a second child with autism.
- The concordance rate among monozygotic twins is high.

Differential diagnosis

- Hearing and visual impairment
- Learning disability
- Global developmental delay
- Physical or sexual abuse
- Primary associated diseases are—prenatal rubella, phenylketonuria, tuberous sclerosis, infantile spasms, postnatal central nervous system (CNS) infections, fragile X syndrome, other metabolic disorders.

Diagnosis

- Diagnosis of autistic disorder is clinical
  - Inappropriate laughing or giggling
  - No fear of dangers
  - Apparent insensitivity to pain
  - Abnormal eye contact
  - Failure to orient to name
  - A lack of interactive play
  - Failure to smile
  - Lack of sharing
  - Lack of interest in other children
  - May prefer to live alone
  - Difficulty in expressing needs. May use gestures
- However, testing for associated neurological disorders such as tuberous sclerosis and fragile X is recommended.

Management

- No uniformly effective therapy
- Behavior therapy
  - Positive reinforcement
  - Self help
  - Social skill training to improve behavior and communication
- Speech therapy
- Occupational therapy
- Early diagnosis and treatment helps the children with autism develop to their full potential. The primary goal of treatment is to improve the overall ability of the child to function. Intensive behavioral therapy, beginning before 3 years of age.

- Medicines (e.g. clomipramine a tricyclic antidepressant) are most commonly used to treat related conditions and problem behaviors, including depression, anxiety, hyperactivity, and obsessive compulsive behaviors.
- Working with the family of an autistic child is vital to the child's overall care.

Prognosis

- Factors associated with better prognosis:
    - Early diagnosis and intensive behavioral therapy.
    - Higher intelligence level.
    - Presence of functional speech.

TIC DISORDERS

CASE

A 6-year-old boy presents with ***eye-blinking***, head shaking, mouth stretching, lateral eye movements and some vocalizations occurring at a frequency of ***several times per minute***.

Definition

- Tic disorderis a sudden, rapid, recurrent, non-rhythmic motor movement or vocalization.
- Tourette syndrome is characterized by multiple fluctuating motor and vocal tics with no obvious cause lasting more than 1 year.

Clinical findings

- Simple motor tics (e.g. eye blinking, neck jerking, shoulder shrugging, and extension of the extremities) are fast, brief movements involving one or a few muscle groups.
- Simple vocal tics (e.g. throat clearing, sniffing, coughing) are solitary, meaningless sounds and noises.
- Onset of tics is typically between ages 4 and 6 years. Peak severity occurs between ages 10 and 12 years.
- Tics evolve slowly, new ones being added to or replacing old ones.
- Some individuals may have tic-free periods of weeks to months.
- Many individuals with mild to moderate tics express little to no distress or functional impairment and may even be unaware of their tics.
- Even individuals with moderate to severe tics can experience little functional impairment, but psychological distress may occur.
- Uncommonly, the presence of tics can lead to social isolation, social victimization, inability to work or attend school, or impaired quality of life.
- Often families are unaware that frequent sniffing, coughing, or blinking may be indicative of tics, attributing these behaviors to medical problems (e.g. allergies, visual problems).

Diagnosis

- A medical workup should be considered for new-onset tics, particularly for presentations characterized by sudden onset, atypicality, or mental status abnormalities.
- Basic laboratory measures (hemoglobin, renal/hepatic function tests, thyroid function tests and ferritin along with urine drug screen for adolescents) should be considered.
- For new sudden (overnight) onset or severe symptom exacerbation, investigations for co-occurring acute infection are needed (e.g. culture, rapid viral tests, etc.).
- Electroencephalogram and brain imaging are not routinely recommended and should be reserved for cases with other neurologic findings that might suggest an autoimmune encephalitis syndrome (limbic encephalitis).
- Co-occurring psychiatric disorders (e.g. ADHD) should be investigated.

Management

- In mild cases, tics are self-limited, and when disregarded disappear.
- When attention is paid to one tic, it may disappear only to be replaced by another that is often worse.
- If the tic and its underlying anxiety or compulsive neuroses are severe, psychiatric evaluation and treatment are needed.
- The most effective medications for treating Tourette syndrome are dopamine blockers.
- However, many pediatric patients can be managed without drug treatment.
- Medications are generally reserved for patients with disabling symptoms.
- Non-pharmacologic treatment of Tourette syndrome includes education of patients, family members, and school personnel (restructuring the school environment to prevent tension and teasing).
- Medications usually do not eradicate the tics. The goal of treatment should be to reduce the tics to tolerable levels without inducing undesirable side effects.
- The two neuroleptic agents used most often are pimozide and risperidone.
- Clonidine, guanfacine, and dopamine modulators have been used in individual patients with some success. Sometimes these agents are used in combination (e.g. clonidine with pimozide).

ANOREXIA NERVOSA AND BULIMIA NERVOSA

CASE

A 15-year-old ***female*** presents with 6 months history of ***absence of menstrual periods***. She complains that she is always cold. There is no history of any illness. She eats an adequate amount of food but is losing weight. She had an intense ***fear of becomingfat***. Her weight was at 70% of ideal body weight ***(extremely thin for her age)***.

Anorexia nervosa

- Body weight <85% of expected from height
- **Fear of weight gain** (becoming obese)
- Disturbed body image (Disturbance of perception of body size, shape and weight)
- Denial
- Attempts to camouflage thinness
- Amenorrhea
- Bradycardia, low BP with pronounced postural drop, long QT interval, and arrhythmias (may cause sudden death)
- Hypothermia
- Fine lanugo hair on body and face
- Dry skin
- Hypokalemia
- Hyponatremia

Bulimia nervosa

- Episodic **binge eating** with inappropriate compensatory behavior (emesis, laxatives, enemas, diuretics, diet pills, fasting, excessive exercise)
- Sense of being out of control during and after attacks
- Disturbed body image
- Body weight usually normal
- Female predominance is in both disorders

Differential diagnosis

- Eating disorder not otherwise specified
- Depression, anxiety disorder
- Sexual abuse
- Inflammatory bowel disease
- Peptic ulcer or gastroesophageal (GE) reflux disease.
- Celiac disease
- Diabetes
- Hyper/hypothyroidism
- Malignancy
- Adrenal insufficiency

Management

- Early intervention and education may prevent full-blown disease.
- Recognize the early signs of anorexia:

  Sudden intense low fat
    - Low carbohydrate diet
    - Complaints of early satiety
    - Failure to join family meals
    - Intense concern over body image
    - Unexplained weight loss
    - Amenorrhea
- Team approach to treatment is most successful with nutritional monitoring, education, family counseling, psychiatric evaluation and treatment, and medical subspecialists as needed.
- Hospitalization may be needed.
- Mortality in anorexia nervosa from suicide, electrolyte disturbance, or cardiac arrhythmia is up to 18% depending upon disease severity.

CHAPTER 06

Pediatric Nutrition and Nutritional Disorders

NUTRITIONAL REQUIREMENTS

- Principle of nutrition depends upon an adequate supply of nutrients required by the body for optimum growth.
- It is important to know the normal nutritional requirements before proceeding onto infant feeding and malnutrition.

Caloric requirement

- Following is the caloric requirement of children at various ages:

Table 6.1: Caloric requirements.

Age	Calories/kg/day
Infants	110
1–3 years	100
4–6 years	90
7–9 years	80
10–12 years	70
13–15 years	60

Formula to calculate the caloric requirements

Up to 10 kg

100 kcal/kg

11–20 kg

1000 kcal+50 kcal/kg for each kg above 10 kg

Above 20 kg

1500 kcal+20 kcal/kg for each kg above 20 kg

Sources of caloric supply

Carbohydrate	50–55%
Fat	30–35%
Protein	10–15%

- The calories in the body are utilized as follows:

Basal metabolic rate (BMR)	50%
Physical activity	25%
Growth	12%
Fecal loss	8%
Specific dynamic action of food	5%

Water requirements

- On an average, water requirement in preschool children is 100–120 ml/kg/day.
- Human needs for water are related to:
    - Caloric consumption
    - Insensible loss
    - Specific gravity of the urine
- An infant needs much larger amounts of water per unit of body weight as compared with an adult.
- The usual food of infants and children is high in water content.

Table 6.2: Average water requirements of children at different ages.

Age	Average body weight (kg)	Total water in 24 hours (ml)	Water/kg/day (ml)
3 days	3.0	250–300	80–100
10 days	3.2	400–500	125–150
3 months	5.4	750–850	140–160
6 months	7.3	950–1100	130–155
9 months	8.6	1100–1250	125–145
1 year	9.5	1150–1300	120–135
2 years	11.8	1350–1500	115–125
4 years	16.2	1600–1800	100–110
6 years	20.0	1800–2000	90–100
10 years	28.7	2000–2500	70–85
14 years	45.0	2200–2700	50–60
18 years	54.0	2200–2700	40–50

Energy substrates

- Energy is needed for the metabolic function that sustains life, for growth, and for physical activity. The rapid growth rate of the infant has higher energy needs.

- Caloric needs can be estimated by summing energy needs for growth, which averages about 5 kcal per gram of weight gain, and for activity, which varies with the work required, with experimentally measured baseline energy needs for the maintenance of life. Such maintenance needs are age and gender specific and are represented by Basal Metabolic Rate (BMR). If energy substrate intake is deficient in an individual, it is expressed as inadequate growth or weight loss.
- Protein, carbohydrates, and fats are used to meet caloric needs, providing 4 kcal, 4 kcal, and 9 kcal respectively for each ingested gram.

Protein

- Protein contributes to energy intake and supplies essential and nonessential amino acids needed for protein synthesis and tissue growth and replacement.
- Essential amino acids are those that must be present in the diet because they are not synthesized at all or in sufficient quantities. Essential amino acids are:
    - Isoleucine
    - Leucine
    - Lysine
    - Methionine
    - Phenylalanine
    - Threonine
    - Tryptophan
    - Valine
    - Histidine (probably)
- Cystine and tyrosine are not synthesized by infants in adequate amounts. Infants also may need taurine.
- Proteins should be provided from any source, which contains all the essential amino acids. The requirement is 2.0–2.5 g/kg/day. These may be obtained from animal sources (milk, meat, fish, egg), which contain all the essential amino acids, or vegetable sources (wheat, dal, rice) which contain 7–14% of proteins.
- Too little protein intake results in kwashiorkor or, if caloric intake is low, marasmus.

Table 6.3: Protein requirements

Age	Protein (gm/kg/day)
Infants	2.5
1–3 years	2.0
4–6 years	1.5
7–12 years	1.0
13–15 years	0.5

Carbohydrates

- Carbohydrates supply the necessary bulk of the diet. They supply most of the body's energy needs.
- In the absence of carbohydrates, body uses proteins and fats for energy.
- Carbohydrates are stored as glycogen in the liver and muscles.

Fats

- Fats are efficient source of energy. They form an integral part of cellular membranes.
- They serve as vehicles for fat-soluble vitamins A, D, E, and K.

Minerals

- Daily requirements of main minerals are given below:

Calcium	0.5–1.5 g/day
Phosphorus	0.5–1.5 g/day
Iron	6–12 mg/day
Sodium	2–3 mEq/kg/day
Potassium	1–2 mEq/kg/day
Magnesium	80–270 mg/day
Iodine	6–15 mg/kg/day
Zinc	10–15 mg/day

Vitamins

- Daily requirements are:

Vitamin A	1500–5000 IU/day
Vitamin B_1	0.5–1.5 mg/day
Vitamin B_2	0.6–1.5 mg/day
Vitamin B_6	0.4–1.4 mg/day
Vitamin B_{12}	1.0–2.5 µg/day
Nicotinic acid	5–20 mg/day
Folic acid	0.2–1 mg/day
Vitamin C	30–35 mg/day
Vitamin D	400 IU/day
Vitamin E	5–15 IU/day

INFANT FEEDING

Principles of feeding

- Feed according to the expected weight.
- Give 110 Kcal/kg body weight per day.
- Give 5 Oz/kg milk feeding per day.
- Water requirement is 150 ml/kg/day.
- Milk should not be diluted after 12 weeks of age.
- No sugar should be added to the bottle feed especially if the baby is also breastfed.
- Weaning food should be started at 4–6 months of age.

BREASTFEEDING

- Human milk is recommended as the exclusive nutrient source for feeding full term infants during the first 6 months after birth and should be continued, with the addition of solid food, at least through the first 12–24 months.
- It is an ideal feeding for infants and has a number of advantages over artificial feeding.

Reflexes concerned with breastfeeding

Reflexes in the baby

- **Rooting reflex:** Just touch the side of face of the baby with the breast and baby will automatically locate the nipple by turning his face. It persists up to 3 months.
- **Sucking reflex:** After placing the nipple into the mouth, infant starts sucking by creating negative intra-oral pressure on the areola of breast. This reflex persists up to 6 months while awake and 9 months while the child is asleep.
- **Swallowing reflex:** After the milk is in the mouth, it is swallowed by a coordinated reflex.

Reflexes in the mother

- **Prolactin reflex:** When infant starts sucking the nipple, nerve impulses travel to the hypothalamus and cause release of prolactin from the anterior pituitary that acts on the breast alveoli and promote milk production.
- **Letdown reflex:** While sucking, impulses also pass onto the posterior pituitary and there is release of oxytocin. It causes contraction of the myo-epithelial cells of the alveoli and milk is forced down the breast. It is known as 'let down reflex' or 'draught reflex'. It is influenced by the higher psychic centers, as it is inhibited in common public places and facilitated by privacy. There is usually no such inhibition in rural mothers who are more familiar with breastfeeding.
- Full fat cow's milk, goat's skim milk, 1% to 2% fat milk, and evaporated milk are not recommended for use during the first 12 months of life.
- Infants fed whole pasteurized cow's milk between 6–12 months of age are at risk of depleting their iron stores and ultimately developing iron deficiency anemia because of the low concentration and bioavailability of iron in cow's milk and possible excessive intestinal blood loss.
- Higher intake of protein, sodium, potassium, and chloride associated with the use of cow's milk inappropriately increases the renal solute load. The small amount of essential fatty acids, as well as vitamin E, zinc, and other trace substances, may not be adequate to prevent deficiencies.
- Skim milks may cause the infant to consume excessive amounts of protein, because large volumes are ingested to satisfy caloric needs.

Table 6.4: Composition of breast milk VS. cow's milk (per 100 kcal).

Composition	Human milk	Cow's milk
Water	87%	87%
Carbohydrate (g)	10.3	7.3
Fat (g)	5	5.7
Protein (g)	1.3–1.6	5.1
Lactalbumin: Casein ratio	60:40	20:80
Sodium (mEq)	1	3.3
Phosphorus (mg)	25	145
Calcium (mg)	50	186
Iron (mg)	0.1	0.08
Osmolarity (mOsm)	11.3	40

Advantages of breastfeeding

- Breast milk is inexpensive. It only requires 500 extra calories for the mother.
- Milk is available all the time and is practically free from pathogenic bacteria. It needs no time for preparation.
- It is available at the optimum temperature.
- Its composition is ideal for infant growth. Its protein is in easily digestible form and it contains high lactose content.
- Breastfeeding is emotionally satisfying for the mother and helps in establishing healthy mother-child relationship.
- It promotes involution of the uterus by secretion of oxytocin.
- It contains immunoglobulinsIgG and IgA and protects against certain infections such as *E.coli*, cholera, gastroenteritis, polio, tetanus, measles, and other viruses. IgA antibodies prevent the microorganisms to adhere the intestinal mucosa. Ingested antibodies from human colostrum and milk provide local GIT immunity against organisms entering the body through GIT.
- It contains Bifidus factor, which promotes the growth of lactobacillus and helps to lower the gut pH. It inhibits the growth of intestinal pathogens, e.g. *E.coli* and yeast.
- Prolonged breastfeeding helps in spacing the children by delaying pregnancy.

Table 6.5: Major protective and anti-inflammatory factors in human milk.

Factors	Function
Immunoglobulins: Secretory IgA, IgM, IgG	Generate immune response to specific antigens
Lactoferrin	Antibacterial effect, especially against Escherichia coli, inhibition of complement, carries iron
Lysozyme	Bactericidal and anti-inflammatory
Casein	Inhibits microbial adhesion to mucosal membranes
Lipids	Protect against enveloped viruses, anti-infective efforts
Prostaglandins	Cytoprotective
Cytokines	Activate the immune system
Glycoconjugates	Antiviral, antibacterial protection
Phagocytes	Absorb pathogens, release IgA
Lymphocytes	Essential for cell-medicated immunity; antiviral activity Memory T cells give long-term protection
Prolactin	Enhances development of B and T lymphocytes Stimulates proliferation of intestinal mucosa
Human growth factors	Mucosal barrier to antigens

- Incidence of breast cancer is less in those mothers who breast-feed their children.
- It contains lactoferrin (an iron-binding whey protein), which inhibits bacterial growth (especially *E.coli*) by depriving them of iron, which is necessary for growth.
- Breast milk is 'species specific' and therefore allergy to breast milk is rare.
- Respiratory and GIT illnesses are significantly less likely to develop or cause death in breastfed infants. Breastfeeding also confers a strong protective effect against *Hemophilusinfluenzaetype b* infection.
- Infants having breastfeeding have decreased incidence of otitis media in the first year of life. There is also decreased incidence of pneumonia, bacteremia, and meningitis.
- Intestinal flora of infants fed on human milk may protect them against infections caused by some species of *E.coli*.
- Human milk is a sufficient source of iron for the first 4–6 months in term infants. Human milk iron is well absorbed as compared to cow's milk.
- Human milk contains a good amount of vitamin C, provided the mother's intake is adequate.

Table 6.6: Conditions for which human milk has been suggested to possibly have a protective effect.

- Diarrhea
- Septicemia
- Recurrent otitis media
- Urinary tract infections
- Necrotizing enterocolitis
- Celiac disease
- Childhood cancer
- Allergy
- Diabetes mellitus
- Obesity
- Hospitalizations
- Infant mortality

Contraindications of breastfeeding

- There are no absolute contraindications to breastfeeding.
- Following are the few relative contraindications.

Maternal

- Chronic debilitating maternal illness, e.g. chronic renal disease, heart failure, active tuberculosis, malnutrition, malignancy, etc.
- If mother is emotionally unstable and unable to feed as in puerperal psychosis.
- Maternal drug intake may affect the infant, e.g. antibiotics, anticonvulsants, and steroids are secreted in the breast milk and can affect the newborn.

Infant

- Breastfeeding is contraindicated (absolutely) in babies having galactosemia or phenylketonuria.

- Prematurity: Premature babies cannot suck breast milk and should be given expressed milk initially.
- Cleft lip or cleft palate: It makes the suction difficult for the infant. It is not a contraindication.

Initiation of breastfeeding

- Mother is most receptive before delivery of a newborn. She should be encouraged to breast feed her baby and motivated for this purpose during antenatal visit.
- During the first few days colostrum is secreted and amount of milk is small (30–40 ml on the 1st day, 100 ml on the 2nd day and around 500 ml on the 12th day).
- For successful lactation, it is necessary that child should be frequently put to the breast, which causes release of essential hormones.
- Feeding should be started within half an hour after delivery.
- The baby should be fed on demand. After a few weeks the baby falls into a routine of feeds.
- Breastfeeding should be given for 5–15 minutes.
- At each feeding both breasts are offered but baby should start the next feed on alternate sides.
- After feeding, baby should be held upright over mother's shoulder to break the wind (burping).

Adequacy of breastfeeding

- Adequacy of breastfeeding is assessed by:

Test Feed

- Weigh the child before and after breastfeeding during a 24 hours period.
- Divide it by number of feeds to see if the baby is getting enough each time.
- This is generally not very practical.

Clinical

- In the first few weeks after birth, an infant is adequately nourished if at least 8–12 feedings are received each day and the infant sleeps contentedly between feedings.
- Gains weight satisfactorily.
- Infants should not refuse to latch on to the breast or be too sleepy to feed.
- Long night-time intervals (>5hours) without feeding should be avoided during the first few weeks.
- Maternal fatigue and anxiety are important contributors to problems with breastfeeding and should be avoided. Family support should be especially helpful in reducing fatigue and anxiety.
- The baby on adequate feed passes a number of stools and urinates a number of times/day.
- During the first day, no more than 24 hours should pass without the infant having urinated or passed a stool. On day 3, breastfed infants usually pass urine three to four times a day and pass one to two stools that are no longer meconium, but are beginning to appear yellow. Later during the first week after birth, the infant should pass urine for about six times per day and pass a yellow stool with each feeding. Later in the month, the stool frequency may diminish to three per day. After this period, several days may pass without a stool for some breastfed infants.

Jaundice and breastfeeding

- Jaundice due to unconjugated hyperbilirubinemia may be associated with breastfeeding during the first week or after the first week.
- During the first week after birth, jaundice in a breastfed infant, may be related to inadequate milk intake and lactation.
- The treatment is aimed at decreasing the enterohepatic recirculation of bilirubin by increasing milk intake through more frequent breastfeeding.

FIVE STEPS TOWARDS GOOD BREASTFEEDING

1. Mother should sit comfortable and relaxed

2. Position the baby

- Baby's neck straight or bent slightly back.
- Baby's body close to the mother's body.
- Baby's whole body supported.
- Baby's facing the breast with nose opposite the nipple.

3. Attach the baby to the breast. The [illegible]

- Touch the baby's lips with her nipple.
- Wait until baby opens her mouth wide.
- Move the baby quickly to the breast with the baby's lower lip well below the nipple.

4. Check for good attachment

- If the baby is well-attached to the breast, there should be:
  - Baby's chin is touching or very close to the breast.
  - Baby's mouth is wide open.
  - Baby's lower lip turned outwards.
  - More areola is visible above than below the mouth.

5. Check for effective sucking

- Baby making slow, deep sucks with pauses for swallowing.

Note: Good positioning of baby is needed for good attachment is required for effective sucking. If signs of good attachment or effective sucking are not present, detach the baby from the breast and start from number 1 again.

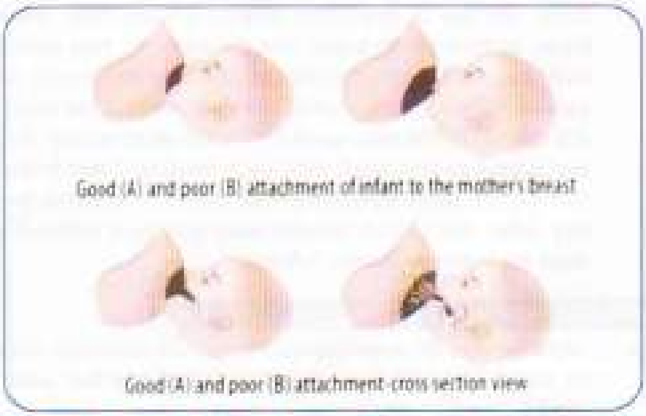

Good (A) and poor (B) attachment of infant to the mother's breast
Good (A) and poor (B) attachment-cross section view

Figure 6.1: Good (A) and poor (B) positions of infant for breastfeeding.

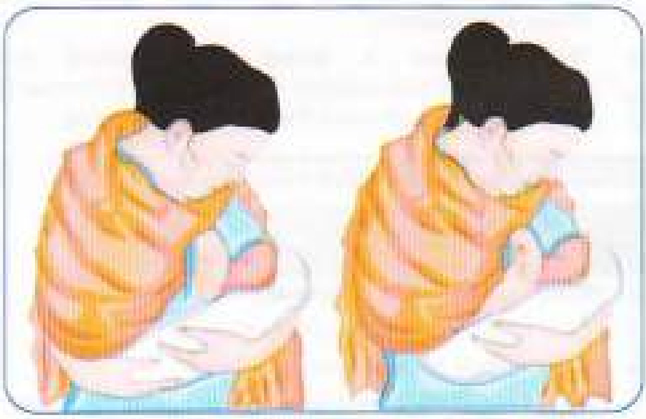


Figure 6.2: Good (A) and poor (B) positions of infant for breastfeeding.

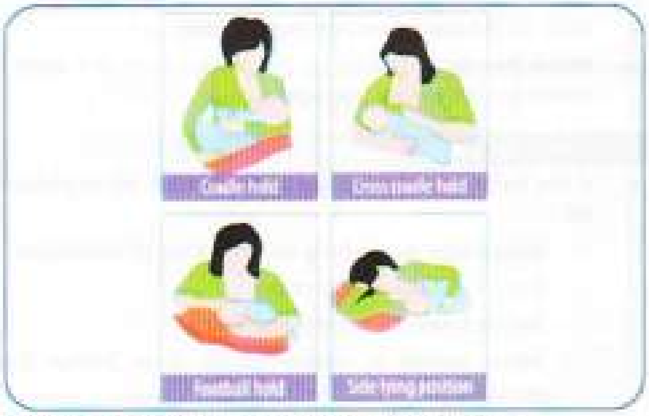

Cradle hold
Cross cradle hold
Football hold
Side lying position

Figure 6.3: Different positions for breastfeeding.

ARTIFICIAL FEEDING

- Formula milks are humanized, i.e. they come very close to the composition of breast milk
- Being expensive, however, cow or buffalo milk is generally preferred.
- Certain formulas are fortified with iron and vitamins.
- Powdered milks are prepared according to the instructions, while cow milk is diluted as follows:

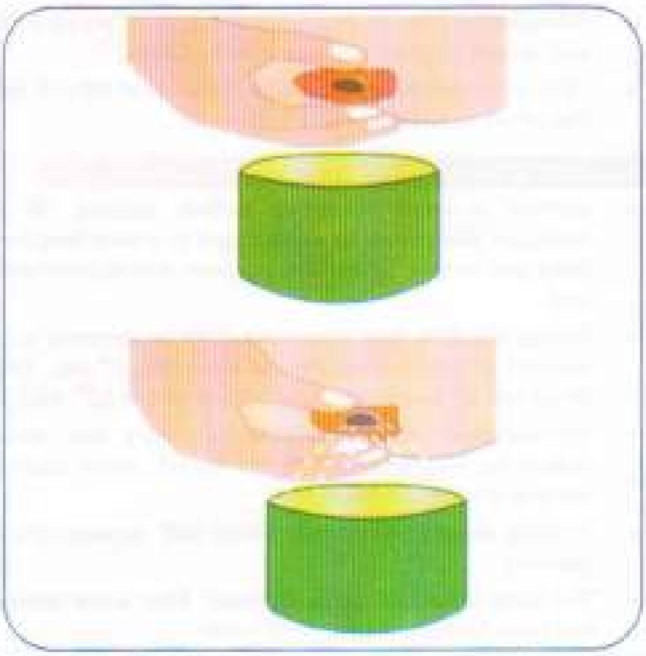


Figure 6.4: C-technique to express breast milk for a baby who is not able to get breastfeeding directly.

Table 6.7: Cow milk feed for new borns.

	Cow milk	Water
First 10 days	1 part	2 parts
10–20 days	1 part	1 part
Up to 2 months	2 parts	1 part

Initiation of feeding

- Feeding should be started within 30 minutes after birth.
- Later start feeding 15 ml milk every 3 hours and increase 15 ml every other day till 150 ml is reached on 7th day of life.

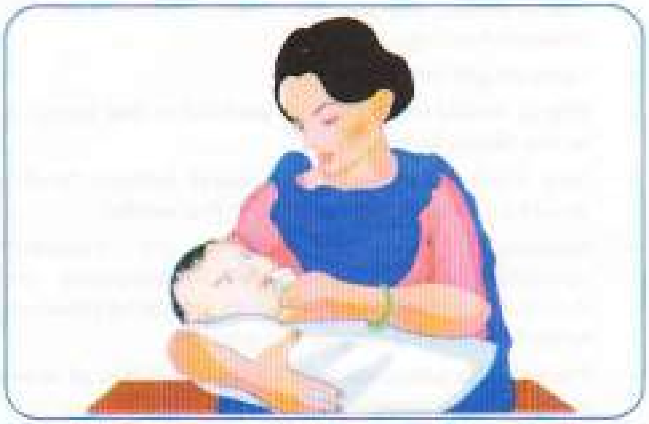


Figure 6.5: Feeding infant with expressed breast milk using a cup.

Calculations

- Work out the caloric requirement (110cal/kg/day and water requirement 150 ml/kg/day).
- Amount of feed:
- Weight in Kg = Number of Oz/feed
- Intervals of feed:

Table 6.8: Intervals of feed.

First 4–6 weeks	2–3 hourly interval
Up to 6 months	4 hourly interval
6–12 months	5 feeds only
1 year onwards	3 feeds only

- If dilution of cow's milk is required, add 1 TSF of sugar to each ounce of water (iso-caloric formula).

Precautions

- Boiled water is used for preparing formula feed and boil all utensils for 5 minutes each time before feeding.
- Or have a few bottles, boil them together and keep in a refrigerator or keep them in the pan with lid on.
- Nipple hole should be large enough to allow milk to fall in drops.
- Bottle should be inverted enough at feeding to prevent entry of air into the nipple.
- Observe for regurgitation of milk and choking for a few minutes.
- Burping is also necessary.

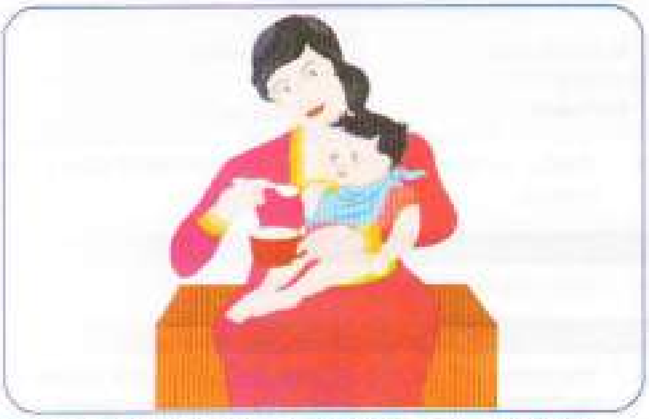


Figure 6.6: Feeding a young child with a cup and spoon.

WEANING

Definition

- It is introducing food other than milk.
- Usually, it is taken in the context of addition of semi-solid feed to the infant's diet.

Time of weaning

- Infants should be weaned at 4–6 months of age.
- When solid food is introduced, single-ingredient food should be chosen and started one at a time at weekly intervals to permit the identification of food intolerance.
- After 4 months, neuromuscular development has advanced sufficiently so pure solids can be swallowed.
- By 8–10 months, the infant accepts finely chopped food, and the likelihood of choking is decreased. Nuts and hard candies should not be given until later in childhood.
- At one year, child requires 3 meals/day and two snacks in between.

Table 6.9: Weaning food at different ages.

Initially give	Mashed banana
At 4–5 months	Cereals as rusk, toast, or bread
6 months	Vegetables like potato
7 months	Egg yolk, minced meat, suji, etc.
At 1 year	Child should eat the same food, which is cooked for rest of the family but with less chilies and spices.

Weaning food

Recipe 1

- It contains approximately 100 calories.
- Get milk (3 Oz) and sugar (1 TSF).
- Add to it 1 TSF of any of the following (Sago, suji, custard, rice, dalia).
- Bring to boil for a few minutes and keep on stirring.

Recipe 2

- It contains approximately 300 calories.
- Get milk (8 Oz) and sugar (2TSF).
- Add 2 tablespoon full of any of the following (rice, dalia, suji, sago).
- Brown the cereals with a little fat, and then add milk and sugar and a cup of water.
- Cook on low fire for further few minutes.

Table 6.10: Caloric value of various food.

Food item	Calories/100 g
Banana	116
Apple	59
Wheat	346
Potato	97
Milk	20/Oz

Sugar	398 (20/TSF)
Vegetable oil	40/TSF
Yogurt	60
Kheer	176
Cheese	348
Butter	729
Ghee	900
Chicken	129
Egg	387 (60/egg)
Fish	399
Biscuits	450 (35/biscuit)
Honey	319
Daalchana	372 (200/plate)
Bread (one small roti)	100

MICRO-NUTRIENTS AND MACRO-NUTRIENTS

- Carbohydrates, protein and fat are called macronutrients.
- Vitamins and minerals are called micronutrients.
- Vitamins are organic compounds essential for normal growth and development. They must be taken in the diet because the body either cannot synthesize them at all or insufficient amounts are synthesized for its needs.
- Vitamins are classified into two groups on the basis of their solubility.

Table 6.11: Vitamin classification.

Fat soluble vitamins	• Vitamin A • Vitamin D • Vitamin E • Vitamin K
Water soluble vitamins	• Vitamin B complex ○ Thiamin (B$_1$) ○ Riboflavin (B$_2$) ○ Niacin ○ Pyridoxine (B$_6$) ○ Cobalamin (B$_{12}$) ○ Folic acid • Vitamin C

VITAMIN A

CASE

A 5-year-old child presents with complaint that she ***cannot see at night***. Her ***skin*** has become ***dry and scaly***. She has complained of headache. She has a 4–5 mm, foamy, mildly vascular, conjunctival lesion next to the cornea on the medial side of both eyes ***(Bitot spot)***.

- Vitamin A deficiency is a major cause of childhood mortality and morbidity, affecting children of less than 5 years in developing countries.
- The prevalence of clinical signs of vitamin A deficiency in developing countries is about 0.6% in preschool children.
- Out of 3.3 million children affected, 2 million are in Asia.
- There is increased risk of death associated with vitamin A deficiency. It occurs well before eye signs appear and is much more wide spread than clinical vitamin A deficiency.
- Provision of a diet rich in vitamin A should be the right strategy. Government of Pakistan/UNICEF has adopted the strategy of supplementation of vitamin A. It involves the use of high dose vitamin A capsule (drops), ideally twice a year.

Table 6.12: Guidelines of the usage of vitamin A.

Age	Vitamin A dose
6–12 months	100,000 units
1–5 years	200,000 units

- Ideally vitamin A should be administered every six months.

Daily requirements

- Daily requirement is 1500 IU/day.

Sources

- Precursors of vitamin A (the carotenes) are found in the yellow and green parts of plants and are especially abundant in carrots.
- The active vitamin is formed by hydrolysis of b-carotene in the intestinal mucosa. Each molecule can produce two molecules of vitamin A, which are absorbed as retinol esters and stored in the liver. Retinol is transported to tissues bound to the a-globulin retinol-binding protein.
- Vitamin A is also present in milk products and eggs. Breast milk and whole cow's milk are satisfactory sources of vitamin A.

Functions

- Vitamin A acts on a number of areas in the human body to facilitate certain processes:
- Maintaining the integrity of epithelial surfaces
- Ensuring adequate structure and function of visual system
- Strengthening the immune system
- Ensuring adequate growth and development
- Helping in efficient utilization of iron for hemoglobin production
- Mucopolysaccharide synthesis
- Mucus secretion
- Vitamin A has long been known as anti-infective vitamin, which is important for normal immune function and the integrity of epithelium of ocular, respiratory and intestinal tissues.
- Vitamin A has a positive impact on mortality and morbidity from diarrhea and measles. This is achieved through an augmenting effect on immunity, cellular differentiation, and maintenance of epithelial surfaces, growth, reproduction and vision.
- Vitamin A deficiency may be an underlying cause of iron deficiency.
- Zinc deficiency may cause immobilization of hepatic vitamin A stores.

Clinical effects of vitamin A deficiency

- Impaired dark adaptation, which is later, followed by night blindness
- Conjunctival and corneal xerosis (dryness)
- Bitot's spots (dry silver-gray plaques on bulbar conjunctiva)
- Keratomalacia (wrinkling and cloudiness of cornea)
- Follicular hyperkeratosis
- Photophobia
- Xerosis (dryness) of skin, keratosis (toad-skin, excessive keratinization of the skin)
- Recurrent episodes of diarrhea and respiratory infections (due to delay in epithelisation of the GIT and respiratory mucosa)
- Retardation of mental and physical growth
- Apathy
- Anemia
- Increased frequency and severity of infections
- Rarely, raised intracranial pressure and hydrocephalus

Table 6.13: WHO xerophthalmia classification.

Classification	Primary signs
X1A	Conjunctivalxerosis
X1B	Bitot spots with conjunctivalxerosis
X2	Corneal xerosis
X3A	Corneal ulceration with xerosis
X3B	Keratomalacia
XN	Night blindness
XF	Xerophthalmia fundus
XS	Corneal scars
XB	Bitots spots

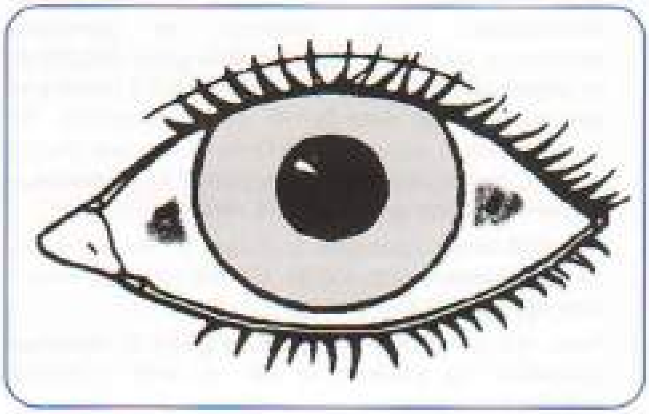


Figure 6.7: Bitot's spot

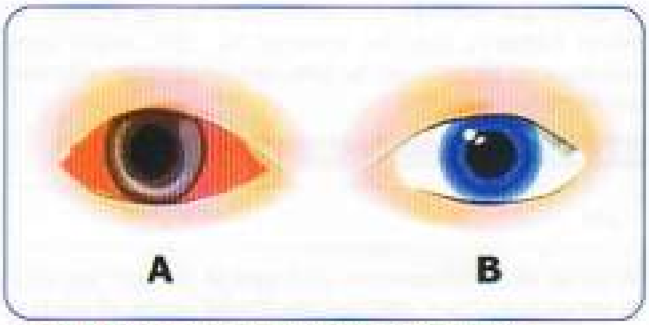


Figure 6.8: Xerophthalmia (A) and normal eye (B).

Diagnosis

- An inquiry into dietary habits can help in establishing the fact that the intake of vitamin A containing food is inadequate
- Clinical evaluation (skin, eyes, growth). For the clinical assessment of the vitamin A deficiency, eye signs are crucial. Such signs only appear when serum retinal levels are less than 0.35 µmol/L
- Dark adaptation test
- Bio-microscopic examination of scraping from conjunctiva or/and vagina
- Plasma carotene concentrations or vitamin A (retinol) levels. Even mild reduction in the serum retinol indicates that the vitamin A stores are being depleted. Serum retinol levels are between 0.35µmmol/L to 0.70 µmol/L

Prevention

- Supplementation in diet of 1500IU/day of vitamin A.
- Protection and promotion of breastfeeding
- Vitamin A supplementation to high risk groups
- Food fortification with vitamin A (vegetable oil, wheat flour)
- Nutritional education, dietary improvement
- Prevention of infections, especially measles and diarrhea

Management

- Any child suffering from severe Protein Energy Malnutrition (PEM), recurrent or persistent gastroenteritis and measles should be given 200,000 IU of vitamin A in a single dose. Infants 6–12 months of age get half the dose (WHO recommendation). No routine dose is required in infants of age less than 6 months, but in case of measles 50,000 IU of vitamin A is given in infants age less than 6 months.
- If a child shows symptoms and signs of the deficiency he should receive 200,000 IU (100,000 IU in less than 1 year age) on day 1, 3, and 14.
- Food rich in vitamin A should be given in abundant quantities, to children at risk or with a clinical deficiency.

Note: We need to improve vitamin A status because it increases the chances of survival. By giving vitamin A, overall mortality may be reduced by 23%, death from measles may be reduced by 50% and death from diarrhea may be reduced by 40%.

VITAMIN D

CASE

A 2-year-old child presents with pain in his right leg. He is on excessive cow milk and has a poor intake of solids. Physical examination reveals ***a failure to thrive child*** with a 3 cm anterior fontanel, a flattened occiput, a prominent forehead, significant dental caries, ***rickets rosary***, bowed extremities, ***widened wrists*** and ankles. Radiographs show a greenstick fracture at the site of pain, along with ***fraying*** at the distal ends of the radius and ulna.

- It is a group of sterols having similar physiologic activity.
- D_2-calciferol is activated ergosterol.
- D_3 is activated 7-dehydrocholesterol in skin (1 mg = 40 IU vitamin D).

Metabolism of vitamin D

- Vitamin D is derived from:
  - Cholecalceferol (Vitamin D_3), formed in the skin by the action of ultraviolet light on 7-dehydrocholesterol. This is the form found in animal tissues, especially the liver.
  - Ergocalceferol (Vitamin D_2), obtained from plants after irradiation.
- In the liver, cholecalciferol is hydroxylated to 25-hydroxy-cholecalciferol (25-OHD_3) by the enzyme 25-hydroxylase. 25-OHD_3 is the main circulating form and store of the vitamin.
- In the proximal renal tubular cells of the kidney 25-OHD_3 undergoes a second hydroxylation, catalyzed by the enzyme 1□-hydroxylase to form the active metabolite, 1,25-dihydroxy-cholecalceferol [1,25-$(OH)_2D_3$].
- 1α-hydroxylase activity, and hence the production of 1,25-$(OH)_2D_3$, may be stimulated by:
  - A low plasma phosphate concentration.
  - An increase in plasma PTH concentration, possibly because of its phosphate lowering effect.
  - Estrogen, prolactin and growth hormone, which increase 1,25-$(OH)_2D_3$ production and which therefore increase calcium absorption during pregnancy, lactation, and growth.
- The kidney is thus an endocrine organ, synthesizing and releasing the hormone 1,25-$(OH)_2D_3$. Impairment of the final hydroxylation vitamin 25-OHD_3 explains the hypocalcemia of the renal disease.
- 1,25-$(OH)_2D_3$ increases calcium absorption by intestinal mucosal cells. In conjunction with PTH, it stimulates osteoclastic activity releasing calcium from bone.

Biochemical actions of vitamin D

- Vitamin D regulates absorption and deposition of calcium and phosphorus by affecting permeability of intestinal membrane.
- The direct effect of vitamin D on bone is similar to that of parathyroid hormone (PTH) and results in bone resorption. Vitamin D also has a direct anabolic effect on bone.
- Vitamin D regulates level of serum alkaline phosphatase, which is concerned with calcium phosphate deposition in bones and teeth.

Sources

- Fish liver oils
- Exposure to sunlight
- Vitamin D fortified milk and margarine

Causes of vitamin D deficiency

- Inadequate direct sun exposure
- High cereal intake
- A vegetarian diet
- Various drugs (phenobarbitone, phenytoin)

Clinical effects of deficiency

- Rickets (high serum phosphate level appears before bone deformities). Rickets will be described in detail in chapter: endocrine and metabolic disorders.
- Infantile tetany
- Poor growth
- Osteomalacia in adults

VITAMIN E

- It is a group of related chemical compounds called tocopherols (1 IU vitamin E = 1 mg alpha-tocopherol).

Characteristics

- It is a fat-soluble vitamin
- It acts as an anti-oxidant
- It may be involved in nucleic acid metabolism

Sources

- Germ oils of various seeds
- Green leafy vegetables
- Nuts
- Legumes

Biochemical actions

- Minimizes oxidation of carotene, vitamin A, and linoleic acid
- Stabilizes membranes

Causes of deficiency

- Deficiency may occur in malabsorption states such as cystic fibrosis, or biliary atresia
- Diets high in unsaturated fatty acids increase the vitamin E requirements in premature infants. Premature infants absorb vitamin E poorly
- Excessive iron administration exaggerates the signs of vitamin E deficiency

Effects of deficiency

- Requirements are related to poly-unsaturated fat intake.
- Deficiency causes red blood cell hemolysis in premature infants and loss of neural integrity. Premature infants have low serum levels of tocopherol and develop hemolyticanemia at 6–10 weeks of age. It is corrected with vitamin E administration.
- Vitamin E deficiency may cause anemia in kwashiorkor.
- In vitamin E deficiency, platelet adhesiveness and platelet counts also increases.
- Patients with malabsorption and vitamin E deficiency develop a degenerative, reversible, neuorologic syndrome characterized by cerebellar ataxia, peripheral neuropathy, and posterior column abnormalities.
- There may be creatinuria, ceroid deposition in smooth muscle, focal necrosis of striated muscle, and muscle weakness.

Diagnosis deficiency

- Blood level of vitamin E is decreased

Prevention

- About 0.7 mg of vitamin E per gram of unsaturated fat in the diet is given daily.
- Children with malabsorption should take more.
- Premature infants are given 15–25 IU/day.

VITAMIN K

- Vitamin K, like many of the B vitamins, can be synthesized by bacteria in the ileum, from which it can be absorbed.
- Vitamin K is a naphtho-quinone that participates in oxidative phosphorylation.

Sources

- Green leafy vegetables
- Liver

Causes of deficiency

- Dietary deficiency does not occur. However, deficiency may occur:
    - In patients with steatorrhea. In such a case, the vitamin whether taken in the diet or produced by intestinal bacteria, cannot be absorbed normally.
    - After administration of some broad-spectrum antibiotics (which may alter the intestinal bacterial flora and so reduce the synthesis of vitamin K, especially in children).
    - In hemorrhagic disease of newborn (see in chapter: Neonatology).
- In the newborn, plasma vitamin K concentrations are low because:
    - Very little can be transported across the placenta.
    - Bacteria capable of synthesizing vitamin K only gradually colonize the neonatal gut.
    - Protein synthesis has not yet reached full adult capacity particularly in premature infants.

Biochemical actions

- Prothrombin formation
- Coagulation factors II, VII, IX and X and osteocalcin are vitamin K dependent
- It is necessary for proteins C, S, and Z formation

Effects of deficiency

- Hemorrhagic disease of newborn
- Hemorrhagic disturbances in children with vitamin K deficiency

Management

- Oral administration of vitamin K corrects prothrombin deficiency. In an infant 1–2 mg/day is given.
- In severe hemorrhage, vitamin K is given parenterally. In such a case, 5 mg/day of vitamin K is given.

VITAMIN B_{12}

- Cyanocobalamin is a water-soluble vitamin.
- Intrinsic factor of stomach is needed for its absorption.

Sources

- It is only found in animal products (e.g. meat, fish, eggs, milk, and cheese).

Biochemical actions

- Transfer of one-carbon units in purine and labile methyl group metabolism
- Essential for maturation of red blood cells in bone marrow
- Metabolism of nervous tissue
- Adenosyl-cobalamin is the coenzyme for methyl-malonyl CoA mutase

Effects of deficiency

- Juvenile pernicious anemia, due to defect in absorption of vitamin B_{12}
- Macrocytic/megaloblasticanemia (see chapter: hematology). It is due to malabsorption of vitamin secondary to celiec disease, inflammatory bowel disease, long term drug therapy.
- Subacute combined degeneration of the spinal cord.
- Methyl-malonicaciduria
- Homocystinuria

Management

- Administer vitamin B_{12} intramuscular 1 mg

FOLIC ACID

- Folic acid (folate) is included in the B group.
- Folic acid is present in green vegetables and meat. It is easily destroyed during cooking and dietary deficiency may occasionally occur.
- It is absorbed throughout the small intestine and clinical deficiency is relatively common in intestinal malabsorption syndromes. In these conditions, low red-cell folate concentrations may be associated with megaloblasticanemia.

Sources

- Main sources are liver, green vegetables, nuts, cereals, cheese, fruits, yeast, beans, and peas

Biochemical actions

- Concerned with formation and metabolism one-carbon units
- Participates in synthesis of purines, pyrimidines, nucleoproteins, and methyl groups

Causes of folate deficiency

- Low dietary intake
- Malabsorption
- Drugs (such as methotrexate, anti-convulsants)

Diagnosis and management

- See megaloblasticanemia in chapter: Hematology

VITAMIN C

> CASE
>
> A 4-year-old girl presents with irritability, miserable condition, ***painful limbs*** (cried when touched her limbs), difficulty in walking, ***easy bruising*** and ***gingival bleeding***. Her ***diet*** is ***deficient in vegetables and fruit***.

Sources

- Ascorbic acid cannot be synthesized by man
- It is found in fruit, particularly citrus fruits, and vegetables

Biochemical actions

- Integrity and maintenance of intracellular material
- Facilitates absorption of iron
- Converts folic acid to folinic acid
- Metabolism of tyrosine to phenylalanine
- Involves in activity of succinic dehydrogenase and serum phosphatase in infants

Pathology

- In vitamin C *deficiency, formation of collagen and* chondroitin sulfate is impaired.
- This leads to defective tooth dentin causing loosening of the teeth.
- Osteoid deficiency causing decreased endochondral bone formation and fractures.
- There is degeneration in skeletal muscles, cardiac hypertrophy, bone marrow depression, and adrenal atrophy.

Effects of deficiency

- Scurvy: Many signs and symptoms of scurvy are related to deficient collagen formation.
- Poor wound healing
- Fragility of vascular walls causes a bleeding tendency, petechiae, and ecchymoses.
- There are swollen, tender, spongy, bleeding gums.
- In infants subperiosteal bleeding and hemarthroses are extremely painful and may lead to premature joint deformities.

- Deficiency of bone matrix causing osteoporosis and poor healing of fractures. In children, bone formation is impaired at the epidiaphyseal junctions, which look 'frayed' radiologically.
- Anemia is due to impaired erythropoiesis.

Scurvy

- Scurvy may occur at any age but it is rare in newborns because the infant is born with adequate stores of vitamin C if the mother's intake has been adequate.
- There are vague symptoms of irritability, tachypnea, digestive disturbances, and loss of appetite.
- There is generalized tenderness especially in legs. Pain results in pseudo-paralysis. Legs assume the typical 'frog position' (hips and knees are semi-flexed with the feet rotated outward). There may be edema along the shafts of the legs.
- A subperiostealhemorrhage can be occasionally palpated at the end of the femur. There are bluish purple, spongy swellings of the mucous membranes of the gums.
- There may be 'rosary' at the costochondral junctions.
- There may be petechial hemorrhages in the skin and mucous membranes.
- Anemia is also common.
- Wound healing is delayed.
- On X-ray of long bones (especially the distal ends of knee):
    - There is ground-glass appearance of bones.
    - Cortex is reduced to 'pencil-point' thinness.
    - Epiphyseal ends are sharply outlined.
    - There is white line of Fraenkel (an irregular but thickened white line at the metaphysis represents the zone of well-calcified cartilage).
    - Epiphyseal centers of ossification have a ground-glass appearance by a white ring.
- Diagnosis is based on:
    - Clinical picture
    - History of poor intake of vitamin C
    - X-ray appearance of long bones
    - Low level of blood vitamin C level
- With adequate treatment, recovery occurs rapidly in infants. Subperiostealhemorrhage may require months to disappear.
- Scurvy is prevented by a diet adequate in vitamin C.
- Daily therapeutic dose of vitamin C is 100–200 mg or more. Daily requirement is 45–60 mg/day in children.

IRON

- Iron deficiency is the most common nutritional deficiency.
- Preterm infants, growth retarded infants, and infants of diabetic mothers are born with low iron stores and are therefore at risk for early iron deficiency.
- Young children are the most susceptible to iron deficiency as a result of an increased iron requirement related to rapid growth during the first 2 years of life and a relatively low iron content in most infant diets.

Consequences of iron deficiency

- The most well-known consequence of iron deficiency is anemia (see iron deficiency anemia in chapter: Hematology).
- Iron deficiency adversely affects child development and behavior. Development deficit to some extent can be corrected with iron treatment.

Specific recommendations

- Full-term breastfed infants need an adequate source of iron by 4–6 months of age (approximately 1 mg/kg/day) preferably from supplementary food. Iron-fortified infant cereal is a good source of iron for initial introduction of an iron containing food. An average of two servings (1/2 oz or 15 g of dry cereal per serving) is needed to meet the daily iron requirements.
- If a full-term breastfed infant is unable to get sufficient iron from dietary sources after 6 months of age, elemental iron (1 mg/kg/day) can be used.
- For preterm or low-birth-weight infants, an oral iron supplement (elemental iron) in the form of drops once a day at 2–4 mg/kg/day at 1 month should be given until 12 months of age.
- Introduce weaning at 4–6 months of age.
- For infants, a good dietary iron source is strained meat. This can be introduced after 6 months of age or when the infant is developmentally ready to consume such food.
- Avoid the use of regular cow, goat or soy milk before 12 months of age. For young children, avoid excessive milk intake, which can displace the desire for food items with greater iron content. A milk intake of 24 oz per day is sufficient to meet the daily calcium requirement of children 1-5-year-old.

Table 6.14: Some important causes of iron deficiency.

- Poor bioavailability
- Excessive dietary phytates, milk, or starch
- Celiac disease
- Inflammatory bowel disease
- Gastrointestinal blood loss (Milk induced enteropathy, varices, ulcers, Meckel's diverticulum)
- Any chronic disease
- Worm infestation
- Trauma

ZINC

> CASE
>
> A 6-month-old baby boy presents with a ***diaper rash*** that is resistant to therapy. There is history of ***intermittent diarrhea***. He is on breastfeeding, and is not taking any solid food. Mother is a vegetarian. On examination, he is thin and listless. There are dry, plaque-like, sharply demarcated lesions***around hismouth and eyes***. Hair is coarse and scanty.

Acrodermatitisenteropathica

- Acrodermatitisenteropathica is an autosomal recessive disorder.
- It is caused by an inability to absorb sufficient zinc from the diet.
- The genetic defect is in the intestinal zinc-specific transporter gene.
- Zinc has a role in numerous metabolic pathways (including those of copper, protein, essential fatty acids, and prostaglandins).
- Zinc is incorporated into many zinc metallo-enzymes.

Clinical findings

- Signs and symptoms usually appear in the first few months of life.
- There is cutaneous eruption characterized by vesiculobullous, eczematous, dry, scaly, skin lesions.
- Skin lesions are symmetrically distributed in the perioral, acral, and perineal areas. Other common sites are cheeks, knees, and elbows.
- Hair is of a peculiar, reddish tint.
- There may be alopecia.
- Other manifestations include:
  - Ocular manifestations (photophobia, conjunctivitis, blepharitis, and corneal dystrophy).
  - Chronic diarrhea
  - Stomatitis
  - Glossitis
  - Paronychia
  - Nail dystrophy
  - Growth retardation
  - Irritability
  - Delayed wound healing
  - Intercurrent bacterial infections
  - Superinfection with *Candida albicans*
- Lymphocyte function is impaired.
- Free radical scavenging is also impaired.
- Chronic zinc deficiency may cause growth retardation and delayed development.

Diagnosis

- A low plasma zinc concentration (less than 50 μg/dL)
- Levels of alkaline phosphatase (a zinc-dependent enzyme) may be decreased
- Histopathologic changes in the skin (parakeratosis and pallor of the upper epidermis)

Management

- Oral therapywith zinc is indicated. Dose is 1-3 mg/kg/day of elemental zinc.
- Zinc therapy rapidly improves the manifestations of the disease.
- The cause of underlying malnutrition should be treated.

IODINE

- Iodine is required for the synthesis of thyroid hormone, which in turn are needed for the regulation of metabolic activities of all cells throughout the life. They are also required to ensure normal growth, especially of the brain, which occurs from fetal life to the end of the third postnatal year.
- Iodine deficiency will impair thyroid function, resulting in a lower metabolic rate, growth retardation and brain damage. Long-term consequences are irreversible mental retardation.
- Iodine deficiency is the most prevalent cause of preventable mental retardation in the world.
- The successful global campaign to iodize all edible salt is reducing the risk associated with this deficiency.

MALNUTRITION

> CASE
>
> A 15 months old boy is brought in emergency with complains of loose motions and vomiting for last three days. His diet is not adequate. On examination her weight is 7.5 kg, mid upper arm circumference (MUAC) 11 cm, length 68 cm.

- Malnutrition is defined as a pathological state resulting from relative or absolute deficiency of one or more essential nutrients.
- **Severe acute malnutrition** is defined as severe wasting and/or bilateral edema.
- Severe wasting in infants of under 6 months of age is marked by visible severe wasting.
- Whereas for children >6 month of age, severe wasting is assessed objectively using anthropometric measurements (weight for length/height, mid-upper arm circumference).
- Severe wasting is extreme thinness diagnosed by a weight-for-length (or height) below −3 SD of the WHO Child Growth Standards.

- In children ages 6–59 months, a mid-upper arm circumference <115 mm also denotes extreme thinness: a color-banded tape is a convenient way of screening children in need of treatment.
- Bilateral edema is diagnosed by grasping both feet, placing a thumb on top of each, and pressing gently but firmly for 10 seconds. A pit (dent) remaining under each thumb indicates bilateral edema.
- To be considered a sign of severe malnutrition, edema must appear in both feet. If the swelling is only in one foot, it may just be a sore or infected foot. The extent of edema is commonly rated in the following way (WHO criteria):

Table 6.15: Grades of bilateral pitting edema with their definition.

Grades of bilateral pitting edema	Definition
Absent	Absent
Grade +	Mild: Both feet/ankles
Grade ++	Moderate: Both feet, plus lower legs, hands and lower arms
Grade +++	Severe: Generalized bilateral pitting edema, including both feet, legs, arms and face

- The simple name protein-energy malnutrition is avoided, as it does not show the complex multi-deficiency etiology.
- Marasmus means (severe wasting), kwashiorkor (characterized by edema), and marasmic kwashiorkor means (severe wasting + edema).
- Every year about 10.6 million children in the world die before 5 years of age. Seven out of 10 of these deaths are due to diarrhea, pneumonia, measles, malaria or malnutrition.
- Malnutrition is primary when there is deficiency of food availability or secondary when food is available but body cannot assimilate it for one or another reason.
- Malnutrition is common in children between the age of 3 months and 3 years but it can also occur earlier or later.
- Mortality is highest in children who are suffering from malnutrition. Malnutrition in infants and preschool children may have a permanent effect on physical growth and development. It may affect mental development also.

Etiology

- Various causes of protein energy malnutrition (PEM) are as follows:

Primary malnutrition

- **Failure of lactation:** Breast milk may become insufficient for the requirement of the child, e.g. if mother becomes pregnant or she is suffering from certain illness.
- **Ignorance of weaning:** Mother's milk is adequate up to the age of 4–5 months when the weaning food should be started. Most mothers are ignorant about weaning food, for not only the time at which to wean but also the type of weaning food to be introduced.
- **Poverty:** Parents may be unable to buy meat, milk, eggs or other high calorie food. In addition, they lack adequate housing, clean water supply and sanitation. All these factors predispose the child to infection and malnutrition.
- **Cultural patterns and food fads:** Cultural factors also influence nutrition. Some mothers instead of giving nourishing food to the child may give him sweets, toffees or tea. Concept of 'hot food' usually results in withdrawal of eggs from the child's diet; similarly banana, citrus fruit and rice are considered to be 'cold food' and withheld from the child's diet. In our male dominated society, best food such as meat, eggs, and fruits are first served to the adult male members of the family and left over are consumed by the women and children.
- **Lack of immunization and primary care:** Repeated infections like diarrhea, respiratory infections are the major factors leading to malnutrition. Lack of medical care results in vicious cycle of infection, malnutrition, and further infections. Lack of immunization against common infectious diseases may result in measles, whooping cough or tuberculosis, sapping energy of the child and resulting in malnutrition.
- **Lack of family planning:** Malnutrition is common in large, poor families where family planning is not practiced. Mother becomes weak following repeated pregnancies, overwork and lack of nutritive food. Malnourished mother in turn gives birth to low birth weight babies who become malnourished later on.

Secondary malnutrition

- It is caused by the infection, malabsorption, congenital malformations or metabolic defects. It is not due to deficiency in the diet.
- **Infections:** Acute, chronic or recurrent infections of the major body systems like gastrointestinal tract, respiratory tract, and urinary tract.
    - Parasitic infestations like worms, parasites (giardia) and malaria
    - Measles, whooping cough
    - Primary tuberculosis
    - Urinary tract infection

- **Congenital diseases:**
    - Heart diseases, e.g. Fallot's tetralogy, ventricular septal defect
    - Congenital lung disease
    - Urinary tract anomalies, e.g. obstructive uropathy
    - Obstruction to CSF flow, e.g. hydrocephalus
- **Malabsorption:**
    - Giardiasis
    - Lactose intolerance
    - Celiac disease
    - Tuberculosis of the intestine
    - Cystic fibrosis
- **Metabolic disorders:**
    - Diabetes mellitus
    - Inborn errors of metabolism
    - Diabetes insipidus
    - Storage diseases
    - Galactosemia
    - Neurodegenerative disorders
- **Psychosocial deprivation**

CLASSIFICATIONS

- Malnutrition is classified by different methods according to the clinical signs, anthropometric measurements and biochemical tests.
- Two clinical syndromes have been widely recognized: marasmus and kwashiorkor.

Gomez (underweight) classification

- In this, weight is assessed at various ages by standard weight charts.
- If weight is less than expected for that age, then child is considered malnourished:

1st degree malnutrition (mild)

- If weight is 75–90% of the expected weight for age.

2nd degree malnutrition (moderate)

- If weight is 60–75% of the expected weight for age.

3rd degree malnutrition (severe)

- If weight is below 60% of the expected weight for age (marasmus).

(This classification is internationally recognized and has the advantage of simplicity for recognition of malnutrition. Its main disadvantage is that it does not consider height and other parameters).

Waterlow classification

- This classification takes into account height of child in addition to his weight.

Table 6.16: Waterlow classification.

Weight for height (WFH)		
90–80% WFH	80–70% WFH	<70% WFH
Mild	Moderate	Severe

- Length is measured for children less than 2 years or less than 85 cm and standing height is measured for children older than 2 years or 85 cm or more.
- A low height-for-age typically reflects socioeconomic disadvantage.
- A low weight-for-height, or wasting, usually indicates acute malnutrition.
- A high weight-for-height indicates overweight.
- How to calculate the weight/height percentage: Example: For a child of 80.5 cm and weighing 8.7 kg, *Weight-for-HeightReference table* give a median weight for a child of this height of 10.9 kg:

  Weight-for-height = (8.7/10.9) x 100 = 80%

Welcome classification

- This classification takes into account the clinical features of edema in addition to weights.

Table 6.17: Welcome classification.

Weight for age	Edema present	Edema absent
80–60% of standard	Kwashiorkor	Ponderal retardation
<60% of standard	Marasmic kwashiorkor	Marasmus

WHO (World Health Organization) classification

Table 6.18: WHO (World Health Organization) classification on Malnutrition.

WHO (wasting) (Low weight for height)	<-2 to >-3 SD	Moderate malnutrition
	<-3	Severe malnutrition
WHO (stunting) (height for age, linear growth)	<-2 to >-3 SD	Moderate malnutrition
	<-3	Severe malnutrition
WHO (wasting) (for age group 6–59 months)	115–125 mm mid-upper arm circumference	Moderate malnutrition
	<115 mm	Severe malnutrition

General classification

- **Mid arm circumference:** It is measured with a measuring tape. It remains constant between 1–5 years of age as fat is replaced by muscle mass. At 12 months it is 16.5 cm. Between 24–48 months it is 12.5–16.5 cm. The cut-off point is considered to be less than 75% of the expected mid-arm circumference and child is labeled as malnourished (<14 cm).
- **Skin fold thickness:** Skin fold thickness is assessed by the Herpendencaliper in the region of triceps or back of shoulders. Normal is between 9–11 mm. If it is less, then patient is considered malnourished.
- **Quac strip:** With the help of a special tape (which has colors on it) the mid arm circumference is measured.

Table 6.19: Color division of Quac strip.

Up to green color	Normal (14 cm)
Yellow color	Borderline malnutrition (14–12 cm)
Red color	Malnourished (<12 cm)

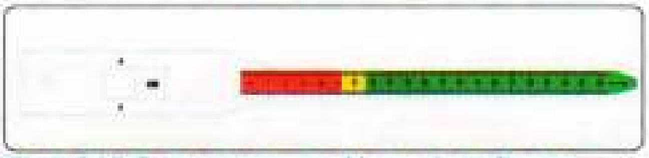


Figure 6.10: Tape to measure mid-arm circumference.

Kanawati classification

- MUAC (mid-upper arm circumference) divided by occipitofrontal head circumference.

Table 6.20: Kanawati classification.

Mild	<0.31
Moderate	<0.28
Severe	<0.25

Cole classification

- It is defined as z-scores (standard deviation or SD) of BMI for age.
- A **Z-score** is the child's height (weight) minus median height (weight) for the age and sex of the child divided by relevant standard deviation.

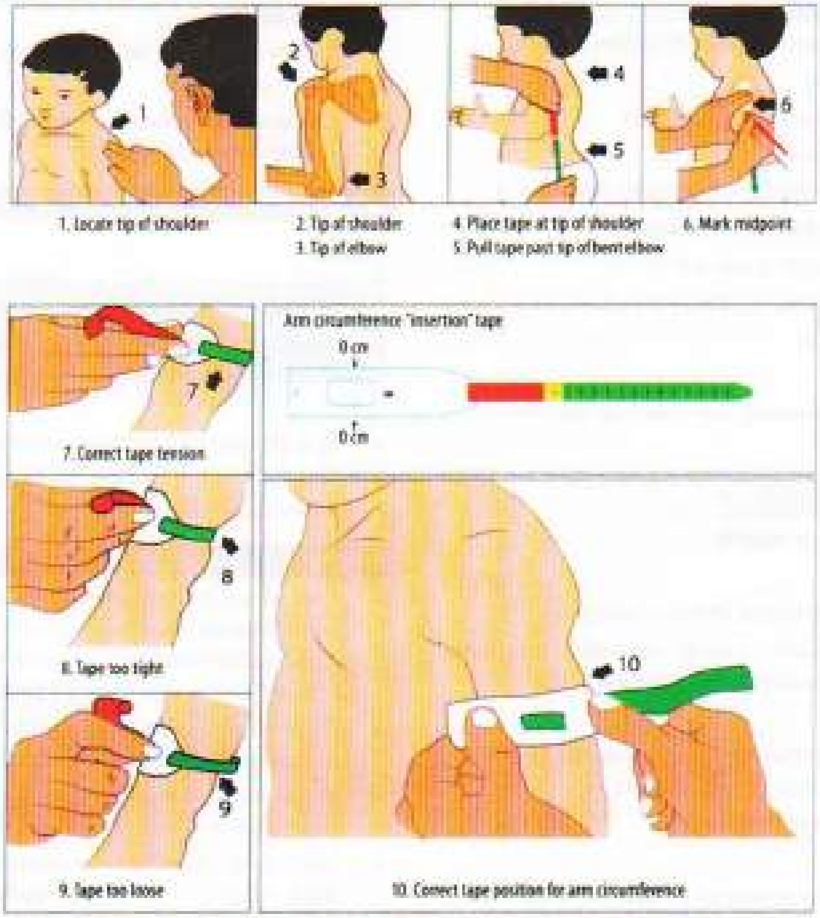

1
2
3
4
5
6
1. Locate tip of shoulder
2. Tip of shoulder
3. Tip of elbow
4. Place tape at tip of shoulder
5. Pull tape past tip of bent elbow
6. Mark midpoint
Arm circumference "insertion" tape
0 cm
0 cm
7
7. Correct tape tension
8
8. Tape too tight
9
9. Tape too loose
10
10. Correct tape position for arm circumference

Figure 6.9: Correct method to measure mid-arm circumference.

Table 6.21: Cole classification.

Grade I	BMI for age z-score (SD) <−1
Grade II	BMI for age z-score (SD) <−2
Grade III	BMI for age z-score (SD) <−3

Body Mass Index (BMI)

- It is calculated by dividing weight in kilograms by the square of height in meters.
- BMI = weight(kg)/height (m^2)
- For children, BMI is age-and gender-specific.
- BMI-for-age can be used from birth to 20 years and is a screening tool for thinness (<−2 SD), overweight (between +1 SD and +2 SD), and obesity (>+2 SD).

Micronutrient deficiencies

- These are another dimension of undernutrition.
- Those of particular public health significance are vitamin A, iodine, iron, and zinc.

Evaluation of the malnourished child

History

- Usual diet before current episode of illness
- Breastfeeding history
- Food and fluids taken in past few days
- Recent sinking of eyes
- Duration and frequency of vomiting or diarrhea
- Appearance of vomit or diarrheal stools
- Time when urine was last passed
- Contact with people with measles or tuberculosis
- Any deaths of siblings
- Birth weight
- Milestones reached (sitting up, standing, etc).
- Immunization

Physical examination

- Weight and length (or height)
- Edema
- Enlargement or tenderness of liver, jaundice
- Abdominal distension, bowel sounds, abdominal splash (a splashing sound in the abdomen)
- Severe pallor
- Signs of circulatory collapse: Cold hands and feet, weak radial pulse, diminished consciousness
- Temperature: Hypothermia or fever
- Thirst
- Eyes: Corneal lesions indicative of vitamin A deficiency
- Ears, mouth, throat: Evidence of infection
- Skin: Evidence of infection or purpura
- Respiratory rate and type of respiration: Signs of pneumonia or heart failure

Investigations

- **Blood glucose:** Glucose concentration <54 mg/dl indicates hypoglycemia.
- **Examination of blood smear by microscopy:** Presence of malaria parasites indicates infection.
- **Hemoglobin or packed cell volume:** Hemoglobin<4 g/dl or packed cell volume <12% indicates very severe anemia.
- **Examination and culture of urine specimen:** Presence of bacteria on microscopy (or >10 leukocytes per high power field) is indicative of infection.
- **Examination of feces by microscopy:** Presence of blood indicates dysentery. Presence of giardia cysts or trophozoites indicates infection.
- **Chest X-ray:** Pneumonia causes less shadowing of the lungs in malnourished children than in well-nourished children. Vascular engorgement is indicative of heart failure. Bones may show rickets.
- **Skin test for tuberculosis:** Often negative in children with tuberculosis or those previously vaccinated with BCG vaccine.
- **Serum proteins:** Not useful in management, but may guide prognosis.
- **Electrolytes:** Rarely helpful and may lead to inappropriate therapy.

MARASMUS

CASE

A 2-year-old child presents with fever, irritability and diarrhea. His weight is 7 kg ***(weight loss)***. There is marked ***muscle wasting***.

- It is 20 times more common than kwashiorkor.
- It usually occurs below 2 years of age but can occur in older children.

Etiology: (Causes of primary malnutrition)

- Marasmus is most commonly due to dietary deficiency or sometime due to severely restricted food intake. Child's diet is deficient in calories, which fails to satisfy the minimum requirement of the rapidly growing child.
- Over diluted milk is given to the child either due to ignorance or from fear of cost.
- Weaning food are not started at all or weaning is done later than 4–5 months of age.
- Infections: Diarrhea, measles, pertussis and primary tuberculosis may cause malnutrition. Mothers may starve the child following the attack of diarrhea for fear of aggravating it.

- Other secondary factors are less frequently responsible for marasmus.

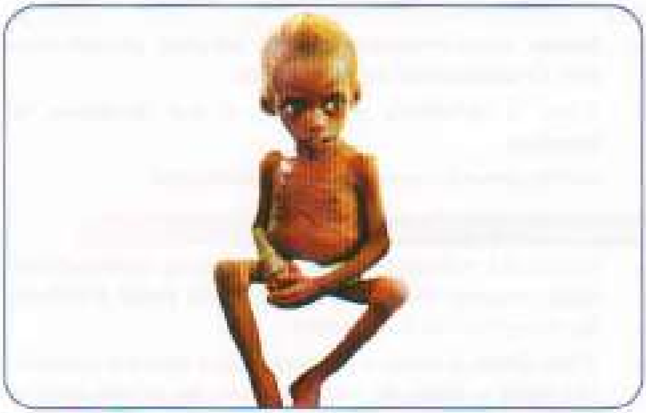


Figure 6.11: Marasmus

Clinical findings

- The clinical picture consists of growth retardation, marked muscle wasting and loss of subcutaneous fat.
- The face is shriveled and has no buccal pad of fat, thighs and buttocks are shriveled and skin becomes loose and hangs in folds.
- Abdomen is protuberant due to hypotonic muscles.
- The temperature is subnormal.
- The tendon reflexes are diminished and plantar reflexes may be absent in extreme cases.
- Child resents being examined but he is usually alert and has a good appetite.
- Edema is never present.
- Skin and hair changes are absent.

Signs always present

- Extreme growth failure and weight below 60% of the expected weight.
- Marked muscle wasting and loss of subcutaneous fat.
- Patient is usually alert and has a good appetite.
- Face is wizened and shriveled like "little old man" or monkey face. There are virtually no buttocks and head seems large in proportion to the body.

Signs occasionally present

- Anemia
- Diarrhea and signs of dehydration
- Signs of vitamins deficiencies, e.g. cheilosis, dermatosis and rickets
- Respiratory infections, tuberculosis and measles may complicate the clinical picture.

Prevention

- Detection and treatment of early malnutrition
- Promote breastfeeding up to the age of 1–2 years
- Avoid artificial feeding till the age of 4–6 months
- Introduce semi-solids at 4–6 months of age
- Immunization and primary care
- Prevention of infective diarrhea, e.g. hand washing

KWASHIORKOR

CASE

A 2 year-old child presents with ***progressiveweight loss*** and ***edema feet***. On examination, there is ***muscular atrophy***, ***loss of skinturgor***, and hypothermia. He has a dark desquamating skin rash over most of the pressure points on the body. His hair is very thin and reddish.

- It usually occurs between 1–5 years of age. But, it can occur earlier or later.
- Edema is always present but does not involve the serous cavities.
- Supply of required calories may be a little less, but proteins are grossly deficient.

Signs always present

- Generalized edema
- Growth failure (wasting masked by edema)
- The child is weak and wasted but has some subcutaneous fat
- Psychomotor changes, e.g. apathy and irritability

Signs usually present

- Hair changes: Hair fine, straight and sparse,discolored.
- Anemia: Inadequate production of RBCs due to:
    - Low iron stores and folic acid
    - Low protein supply due to malnutrition
    - Hookworm infestation
    - Malaria
- Loose stools due to
    - Infective diarrhea
    - Secondary lactase deficiencies

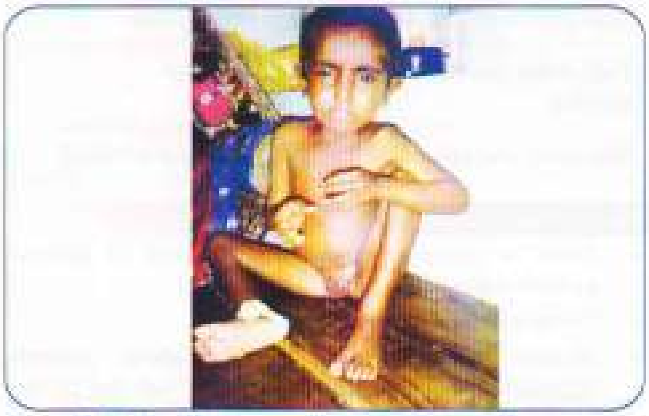


Figure 6.12: Kwashiorkor

Signs occasionally present

- Skin:

- 'Flaky Paint' dermatitis and either hypopigmentation or hyperpigmentation on covered areas
    - Ulcers or open sores may be present
    - Signs of vitamin deficiencies
- Liver:
    - Liver is enlarged due to fatty infiltration

Complications

- Hypothermia
- Hypoglycemia
- Cardiac failure (shock)
- Infections
- Vitamin A deficiency (corneal clouding and ulceration)
- Severe anemia
- Dermatosis
- Watery diarrhea and/or vomiting and dehydration
- Abdominal distension

Table 6.22: Difference between marasmus and kwashiorkor.

Kwashiorkor	Marasmus
Under weight	Extremely under weight below 60%
Edema is always present	Edema is absent
Thin lean muscles, fat is present	Muscle wasting and loss of subcutaneous fat
Puffy, moon face	Appearance (simian) monkey face
Hair changes are present	Hair are normal
Miserable looking and apathetic	Face alert
Poor appetite and anorexic	Appetite is better
Flaky-Paint dermatitis present	Skin is normal
Skin shiny and edematous	Skin loose and wrinkled

Biochemical changes

- There is hypoproteinemia and reversal of albumin globulin ratio.
- There is ketonuria due to starvation.
- Glucose tolerance curve is like diabetic patients. Although peak blood sugar is not very high but decline of blood sugar is very slow.
- There is aminoaciduria.
- Plasma amino acids are low.
- Urinary excretion of hydroxyproline is less as compared to creatinine.
- Serum cholesterol is low.
- Serum cholinersterase, lipase, alkaline phosphatase and 17-ketosteroid are decreased.
- There is deficiency of vitamin K and tendency for bleeding.
- Serum growth hormone level is increased.

Management in severe malnutrition

- Successful management of the severely malnourished child requires that both medical and social problems be recognized and corrected.
- If the illness is viewed as being only a medical disorder, the child is likely to relapse when he or she returns home, and other children in the family will remain at risk of developing the same problem.

Initial Treatment: (2–3 days)

- Life-threatening problems (hypoglycemia, hypothermia, infection and fluid electrolyte balance) are identified and treated in a hospital.
- Specific deficiencies are corrected.
- Metabolic abnormalities are corrected.
- Feeding has begun.

Rehabilitation

- Early rehabilitation (3–7 days)
- Late rehabilitation (2–6 weeks)
- Intensive feeding is given to recover most of the lost weight.
- Emotional and physical stimulation are increased.
- The mother is trained to continue care at home.
- Preparations are made for discharge of the child.

Follow-up: (4–6 months)

- After discharge, the child and the child's family are followed to prevent relapse and assume the continued physical, mental and emotional development of the child.

Emergency treatment (first phase)

- Initial treatment begins with admission to hospital and lasts until the child's condition is stable and his/her appetite has returned, which is usually after 2–7 days. If the initial phase takes longer than 10 days, the child is failing to respond.
- The principal tasks during initial treatment are:
- To treat or prevent hypoglycemia
- To treat and prevent hypothermia
- To treat or prevent dehydration and restore electrolyte balance
- To treat incipient or developed septic shock, if present
- To start feeding the child

- To treat infection
- To identify and treat any other problem, including vitamin deficiency, severe anemia, and heart failure
- These patients require hospitalization and need careful evaluation for complications like dehydration and acute infections, which may threaten life
- Give oxygen, IV glucose, and IV fluids for shock
- Main principles of management are given below

Fluids and electrolyte balance

- Intravenous rehydration (IV infusion) is only indicated in a severely malnourished child with circulatory collapse caused by severe dehydration or septic shock. IV fluids can easily cause fluid overload and heart failure in a severely malnourished child (only give IV fluids to children with signs of shock).
- Use one of the following solutions (in order of preference):
    - Ringer's lactate solution with 5% dextrose
    - Normal (0.9%) saline with 5% dextrose
    - Half-strength Darrow's solution with 5% dextrose
- Give 15 ml/kg intravenous over 1 hour and monitor the child carefully for signs of over-hydration.
- Reassess the child after 1 hour.
- If the child is severely dehydrated, repeat the IV treatment (15 ml/kg over 1 hour) and the switch to ReSoMal orally or by NG tube. There should be an improvement with IV treatment and his or her respiratory and pulse rates should fall.
- In this case, if the child fails to improve after the first IV treatment and his or her radial pulse is still absent, then assume that the child has septic shock and treat accordingly.
- ReSoMal is a rehydration solution for children with severe acute malnutrition (SAM). It is a modification of the standard Oral Rehydration Solution (ORS) recommended by WHO. ReSoMal contains less sodium, more sugar, and more potassium than standard ORS and is intended for severely malnourished children with diarrhea. It should be given by mouth or by nasogastric tube. Do not give standard ORS to severely malnourished children.
- Contents of ReSoMal as prepared from standard ORS:

Water	2 liters
WHO-ORS	one 1 liter packet
Sugar	50 g
Mineral mix solution	40 ml or one leveled scoop CMV (combined mineral mix)

- For a child who has dehydration but no sign of shock, give ReSoMal as follows, in amounts based on the child's weight:

Table 6.23: Amount of ReSoMal to be given to the patient.

How often to give ReSoMal	Amount to give
Every 30 minutes for first 2 hours	5 ml/kg body weigh
Every hour for up to 10 hours	5-10 ml/kg

- The amount offered in this range should be based on the child's willingness to drink and the amount of ongoing losses in the stool.
- If the child has already received IV fluids for shock and is switching to ReSoMal, omit the first 2-hour treatment and start with the amount for the next period of up to 10 hours.
- Replace ongoing loss with 30 ml of ReSoMal per **watery stool** for edematous children and with 50–100 ml for non-edematous children under 2 years and 100 to 200 ml for non edematous children 2 years and above.

Hypoglycemia

- All severely malnourished children are at risk of developing hypoglycemia (blood glucose <54 mg/dl). It is an important cause of death during the first 2 days of treatment.
- Hypoglycemia may be caused when:
    - A serious systemic infection is present.
    - A malnourished child has not been fed for 4–6 hours.
- To prevent hypoglycemia, the child should be fed at least every 2–3 hours day and night.
- Signs of hypoglycemia are low body temperature (<36.5°C), lethargy, drowsiness, limpness, loss of consciousness, sweating and pallor usually do not occur in malnourished children with hypoglycemia.
- If hypoglycemia is suspected, treatment should be given immediately without laboratory confirmation. It will give no harm, even if the diagnosis is incorrect. In a conscious child, give 50 ml of 10% glucose or sucrose. Stay with the child until he/she is fully alert. If the child is losing consciousness and cannot take orally, give 5 ml/kg sterile 10% glucose IV, followed by 50 ml of 10% glucose or sucrose by Nasogastric (NG) tube. If IV glucose cannot be given immediately, give the NG dose first. Continue frequent oral or NG feeding to prevent a recurrence.

Control of Infection

- Infections such as tuberculosis, urinary tract infection and septicemia should be treated. Antibiotics are usually used to control infection.

- Give all severely malnourished children antibiotics for presumed infection even if they do not have clinical sign of systemic infections. Give the first dose of antibiotics while other initial treatments are going on, as soon as possible.
- Children with no apparent signs of infection and no complications should be given amoxicillin or cotrimoxazole orally for 5 days.
- Children with complications (septic shock, hypoglycemia, hypothermia, skin infections, respiratory or urinary tract infections, or who appear lethargic or sickly) should be given: Ampicillin (50 mg/kg IM or IV every 6 hours for 2 days), followed by amoxicillin (15 mg/kg orally every 8 hours for 5 days) and gentamicin (7.5 mg/kg IM or IV once daily for 7 days.
- If the child fails to improve within 48 hours, add ceftriaxone 100 mg/kg divided into 2 doses IV or IM for 5 days.
- If specific infections are identified which require a specific antibiotic not already being given, give an additional antibiotic to address that infection. For example, dysentery may require additional antibiotics. Certain skin infections such as candidiasis require specific treatment. Antimalarial treatment should be given accordingly.

Hypothermia

- A severely malnourished child is hypothermic if the rectal temperature is below 35.5°C or if the axillary temperature is below 35°C.
- Infants and children with marasmus are highly susceptible to hypothermia due to large areas of damaged skin or serious infections.
- If the underarm temperature is below 35°C (95°F), the child should be warmed.
- Following techniques may be used to warm the child:
    - ○ Kangaroo technique by placing the child on the mother's bare chest or abdomen (skin-to-skin) and covering both of them.
    - ○ Clothe the child well (including the head), cover with a warmed blanket and place an incandescent lamp over, but not touching, the child's body.
- Temperature must be measured every 30 minutes during rewarming with a lamp to prevent hyperthermia.
- All hypothermic children must also be treated for hypoglycemia and for serious systemic infections.

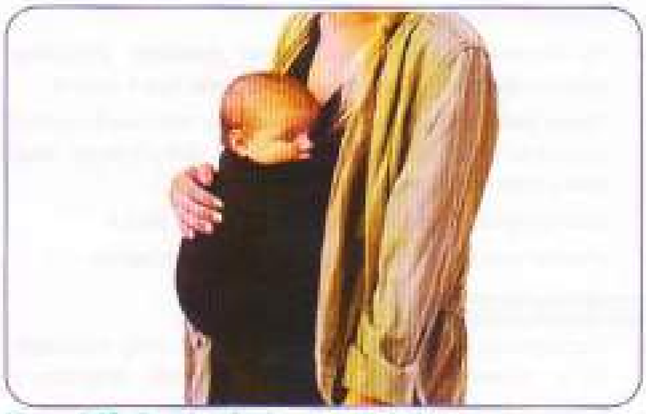


Figure 6.13: Position for kangaroo mother care.

Severe anemia

- Severe anemia is a hemoglobin concentration of <4 g/dl (or hematocrit<12%). If it is not possible to test hemoglobin, rely on clinical judgment.
- Severe anemia can cause heart failure and must be treated with a blood transfusion. As malnutrition is usually not the cause of severe anemia, it is important to investigate other possible causes such as malaria and intestinal parasites (for example, hookworm).
- Give blood transfusion in the first 48 hours if:
    - ○ Hb is <4 g/dl, (Hct is <12%), or
    - ○ Hb 4 to 6 gm/dl (Hct 12 to 18%) and respiratory distress.

Corneal clouding and ulceration

- Corneal clouding and ulceration are dangerous conditions that may lead to loss of vision if not treated urgently.
- Give vitamin A and atropine eye drops immediately for corneal ulceration.
- Vitamin A dose is given in next table.
- You should instill one drop atropine (1%) into the affected eye(s) to relax the eye and prevent the lens from pushing out. Tetracycline eye drops and bandaging are also needed (WHO recommendation).

Dietary management

- The principle of dietary treatment is adequate amount of protein and calories.

Table 6.24: Average dietary requirement.

Caloric requirement	120–140 cal/kg/day
Protein requirement	3–5 gm/kg/day
Elemental iron	6 mg/kg/day
Vitamin A	• Age <6 months (50,000 IU). • Age 6–12 months (100,000 IU).

	• Age >12 months (200,000 IU).
Vitamin D	4000 IU daily
Vitamin K	5 mg IM or IV once daily

- Initially, small frequent feeds are given as these patients are anorexic and prone to vomiting. Tube feeding is required in severe cases.
- Milk is one of the best form for providing both calories and proteins.
- After 7–10 days of dietary management, solid feeds are required for children older than 4–6 months. These include dalia, khichri, feerni and eggs.
  - In first 3–4 days, give 90–150 ml/kg skimmed milk or half diluted cow's milk.
  - Three to four days later, add one solid feed per day.
  - Add another solid feed/day after another 3–4 days later.
  - By 20th day of rehabilitation, add three solid feeds/day.
- What is reductive adaptation? The systems of the body begin to "shut down" with severe malnutrition. The systems slow down and do less in order to allow survival on limited calories. This slowing down is known as reductive adaptation. As the child is treated, the body's systems must gradually "learn" to function fully again. Rapid changes (such as rapid feeding or fluids) would overwhelm the systems, so feeding must be slowly and cautiously increased.

Feeding formulas

F-75 and F-100

- F-75 is the starter formula to use during initial management, beginning as soon as possible and continuing for 2–7 days until the child is stabilized.
- Severely malnourished children cannot tolerate usual amounts of protein and sodium at this stage, or high amount of fat. They may die if given too much protein or sodium. They also need glucose, so they must be given a diet that is low in protein and sodium and high in carbohydrate.
- F-75 is especially made to meet the child's needs without overwhelming the body's systems in the initial stage of treatment.
- Use of F-75 prevents deaths.
- F-75 contains:
  - 75 kcal
  - 0.9 g protein/100 ml
- As soon as the child is stabilized on F-75, F-100 is used as a catch-up formula to rebuild wasted tissues.
- F-100 contains more calories and protein:
  - 100 kcal
  - 2.9 g protein/100 ml

Mineral mix

- Mineral mix is included in each recipe for F-75 and F-100. It is also used in making ReSoMal.
- The mix contains potassium, magnesium, and other essential minerals.

Table 6.25: Examples of recipes for F-75 and F-100.

If you have cereal flour and cooking facilities, use one of the following recipes for F-75			
Alternatives	Ingredients	Amount for F-75	
If you have dried whole milk	Dried whole milk	35 g	
	Sugar	70 g	
	Cereal flour	35 g	
	Vegetable oil	20 g	
	Mineral mix	20 ml	
	Water to make 1000 ml	1000 ml	
If you have fresh cow's milk	Fresh cow's milk	300 ml	
	Sugar	70 g	
	Cereal flour	35 g	
	Vegetable oil	20 g	
	Mineral mix	20 ml	
	Water to make 1000 ml	1000 ml	
If you do not have cereal flour, or there are no cooking facilities, use one of the following recipes for F-75. No cooking is required for F-100			
Alternatives	Ingredients	Amount for F-75	Amount for F-100
If you have dried whole milk	Dried whole milk	35 g	110 g
	Sugar	100 g	50 g
	Vegetable oil	20 g	30 g
	Mineral mix	20 ml	20 ml
	Water to make 1000 ml	1000 ml	1000 ml

If you have fresh cow's milk	Fresh cow's milk	300 ml	880 ml
	Sugar	100 g	75 g
	Vegetable oil	20 g	20 g
	Mineral mix	20 ml	20 ml
	Water to make 1000 ml	1000 ml	1000 ml

Re-feeding syndrome

- It occurs if aggressive carbohydrates are given. There is an increased insulin level resulting in shifting of potassium, phosphate and magnesium into the cells.
- The severe hypophosphotemia during re-feeding produces weakness, rhabdomyolysis, neutrophil dysfunction, cardio-respiratory failure, seizures, altered level of consciousness or sudden death.

Rehabilitation

- Rehabilitation phase is started when the child's appetite has returned.
- A child who is still on NG tube feeding is not considered ready to enter the rehabilitation phase.
- **Principles of management:** Principle tasks during rehabilitation phase are:
  - To encourage the child to eat as much as possible
  - To re-initiate and/or encourage breastfeeding as necessary
  - To stimulate emotional and physical development
  - To prepare the mother to continue to look after the child after discharge
- **Criteria for transfer to nutritional rehabilitation:** Child should remain in hospital for the first part of the rehabilitation phase. The child should be transferred to nutritional rehabilitation when all the criteria given below have been met (usually 2–3 weeks after admission).
  - Eating well
  - Mental state has improved: smiles, responds to stimuli, interested in surroundings
  - Sits, crawls, stands or walks (depending on age)
  - Normal temperature (36.5–37.5°C)
  - No vomiting or diarrhea
  - No edema
  - Gaining weight: >5 g/kg of body weight per day for 3 successive days
- **Nutritional rehabilitation:**
  - The most important determinant of the rate of recovery is the amount of energy consumed.
  - Infants under 24 months can be fed exclusively on liquid or semi-liquid diets. Older children can be given solid food.
  - Nearly all severely malnourished children have anemia and should be given supplementary folic acid and iron. Iron should never be given during the initial phase of treatment, but must be given during the rehabilitation phase. Giving iron early in treatment can have toxic effects and interfere with the body's ability to resist infection. Iron is given in a dose of 3 mg/kg/day in 2 divided doses for 3 months. Folic acid is given 5 mg on day one and then 1 mg/day thereafter.
  - Child should be weighed daily. The usual weight gain is about 10–15 g/kg/day. A child who does not gain at least 5 g/kg/day for 3 consecutive days is failing to respond to treatment. With high energy feeding, most severely malnourished children reach their target weight for discharge after 2–4 weeks.
- **Recovery:** As described above, recovery takes place in two stages:
  - Initial recovery occurs in 2–3 weeks when edema disappears and other signs improve.
  - Consolidation phase: In next 2–3 months, child regains normal weight and is considered clinically recovered.
- **Criteria for discharge from hospital:**

1. Child:
   - Weight gain is adequate (at a normal or increased rate).
   - Eating an adequate amount of nutritious diet that the mother can prepare at home.
   - All vitamin and mineral deficiencies have been treated.
   - All infections and other conditions have been or are being treated, including anemia, diarrhea, intestinal parasitic infections, malaria, tuberculosis, and Otitis media.
   - Full immunization program started.

(All children from 9 months who are not vaccinated should be given measles vaccine both on admission and discharge. The first measles dose often does not give a protective antibody response. It is given because it ameliorates the severity of incubating measles and partially protects from nosocomial measles. The second dose is given to provoke protective antibodies).

2. Mother:
   - Able and willing to look after the child
   - Knows how to prepare appropriate food and to feed the child
   - Knows how to make appropriate toys and to play with the child
   - Knows how to give home treatment for diarrhea, fever, and ARI, and how to recognize the signs that mean she must seek medical assistance

- Should be counseled strongly on exclusive breastfeeding

3. Health worker:
    - Able to ensure follow-up of the child and support for the mother

Table 6.26: Low weight gain during rehabilitation.

Poor	<5 g/kg/day
Moderate	5–10 g/kg/day
Good	>10 g/kg/day

Follow up

- Planned follow up of the child at regular intervals after discharge is essential.
- As the risk of relapse is greatest soon after discharge, the child should be seen after 1 week, 2 weeks, 1 month, 3 months, and 6 months.
- If a problem is found, visits should be more frequent until it is resolved.
- After 6 months, visits should be twice yearly until the child is at least 3-year-old.

Management in mild and moderate cases

- These patients respond rapidly to dietary therapy unless they have gastroenteritis or other infections.
- Mainstay of treatment is enough food, which is prepared fresh and is not contaminated.
- Milk alone is adequate for 4–6 months old infant while weaning food are given to older children.
- Their requirements are:
    - Calories 120 Cal/kg/day
    - Protein 2–3 g/kg/day
    - Vitamin A 1500 IU/day
- Other requirements are same as for severe PEM patients.

OBESITY AND OVERWEIGHT

CASE

A 12-year-old boy presents for evaluation of obesity. Physical examination is ***normal*** but his ***weight*** is 67 kg ***(99.6th centile)*** and height 151 cm (75th centile) giving a BMI of 29 (obese).

- Body Mass Index (BMI) is used as a screening tool to identify possible weight problems in children.
- It is calculated by dividing weight in kilograms by the square of height in meters.

Definition

- BMI (body mass index) between the 85th and 95th percentiles indicates overweight.
- BMI >95th percentile indicates obesity.

Main points

- Many obese children become obese adults, and the risk of remaining obese increases with age and degree of obesity.

Table 6.27: Time frame for the management of the child with severe malnutrition.

Activity	Initial treatment days 1–2	 days 3–7	Rehabilitation weeks 2–6	Follow-up weeks 7–26
Treat to prevent:				
hypoglycaemia	------------------------>			
hypothemia	------------------------>			
dehydration	------------------------>			
Correct electrolyte imbalance	-->			
Treat infection	-->			
Correct micronutrient deficiencies	<-------------- without iron ------- with iron ---------------> --->			
Begin feeding	-->			
Increase feeding to recover lost weight ("catch-up growth")		-->		

- Obesity runs in families and is rarely related to genetic influences.
- There is an association between obesity and television watching and excessive dietary intake.
- Children born to obese mothers are three to five times more likely to be obese in childhood.
- Some small for gestational age (SGA) newborns have higher risks for abnormal postnatal weight gain and diabetes.

Table 6.28: BMI for Age-Weight Status Categories.

A BMI Percentile of:	Suggests that a child is:
Less than the 5th percentile	Underweight
5th percentile to less than the 85th percentile	Healthy Weight
85th to less than the 95th percentile	Overweight
Equal to or greater than the 95th percentile	Obese

Complications

- High BMI increases the risk of metabolic and cardiovascular diseases, some cancers, and diabetes.

Medical complications of pediatric obesity

- Hypertension (2.9 times higher in obese children)
- Type 2 diabetes (2.9 times higher in obese children)
- Coronary artery disease
- Hypercholesterolemia (2.1 times higher)
- Other hyperlipidemias
- Left ventricular hypertrophy
- Obstructive sleep apnea
- Increased severity of asthma
- Mechanical stress on joints, slipped capital femoral epiphysis
- Hepatic steatosis, cholelithiasis
- Gastroesophageal reflux
- Insulin resistance, acanthosisnigricans
- Social stigma (depression, low self-esteem)

Diagnosis

- **BMI** (body mass index:
- BMI = wt (kg) / Ht (m^2)
- Early recognition of excessive rates of weight gain, overweight, or obesity in children is essential.
- Routine evaluation should include the following:
  - **Anthropometric data,** including weight, height, and calculation of BMI
  - **Dietary and physical activity history**
  - **Physical examination.** Assess blood pressure, adiposity distribution (central versus generalized), markers of comorbidities (acanthosisnigricans, hirsutism, hepatomegaly, orthopedic abnormalities), and physical stigmata of a genetic syndrome.
  - **Laboratory studies.** Screening for cholesterol, hemoglobin A1c, fasting lipid profile, fasting glucose levels, liver function tests, and thyroid function tests (if there is a faster increase in weight than height).

Prevention

- Changes in dietary and physical activity patterns should be made.
- The importance of physical activity should be emphasized. Increasing walking, using stairs, and biking to school.
- Avoid fast food and promote healthy eating patterns.
- Promote of breastfeeding during infancy.
- Excessive juices or soda in diet should be removed.
- Children should never be forced to eat when they are not willing.
- Overemphasis on food as a reward should be avoided.
- Balanced food to be offered on a regular basis, including fruits, vegetables, grains, protein, and dairy.
- Time spent in sedentary behavior, such as television viewing and video/computer games, should be limited.

Management

- More aggressive treatment is needed only for those who have not responded to above preventive interventions.
- Treatment includes a multidisciplinary approach.

CHAPTER 07

Fluid and Electrolyte Disorders

MAINTENANCE FLUID THERAPY

Maintenance fluids

- The amount of fluid needed to maintain normal body function is directly related to caloric expenditure, which in turn is related to a child's weight.
- **Maintenance fluids:** Maintenance intravenous (IV) fluids are needed in children who cannot feed enterally.
- **Replacement fluids:** Children may require concurrent replacement fluids, along with maintenance fluids if they have excessive ongoing losses e.g. vomiting, diarrhea or excessive drainage from a nasogastric tube.
- **Deficit fluid:** If dehydration is present, the patient also needs deficit replacement fluid.
- Maintenance fluids are composed of a solution of water, glucose, sodium, potassium, and chloride. Glucose in maintenance fluids provides approximately 20% of the normal caloric needs of the patient.
- Maintenance fluids do not provide adequate calories, protein, fat, minerals, or vitamins.
- Daily water losses are urine, stool, and insensible lossesfrom the skin and lungs. Failure to replace these losses leads to dehydration.

Table 7.1: Body weight method for calculating maintenance fluid volume and rate.

Body weight (Kg)	Volume per day	Hourly rate
0–10	100 ml/kg	4 ml/kg/h
11–20	1000 ml + 50 ml/kg for each 1 kg >10 kg	40 ml/h + 2 ml/kg/h × (wt–10)
>20	1500 ml + 20 ml/kg for each 1 kg >20 kg	60 ml/h + 1 ml/kg/h × (wt – 20)

- The maximum total fluid per day is normally 2400 ml.
- The maximum fluid rate is normally 100 ml/hour.
- Sodium and potassium are given in maintenance fluids to replace losses from urine and stool.
- For each 100 ml of maintenance fluids, a child needs 3 mEq of sodium and 2 mEq of potassium.
- First, calculate the water and electrolyte needs.
- Then, give either 5% dextrose (D5) in ¼normal saline (NS) plus 20 mEq/L of potassium chloride (KCl) or D5 in ½ NS plus 20 mEq/L of KCl.
- Children weighing less than 10 kg are best treated with the solution containing ¼ NS (38.5 mEq/L) because of their high water needs per kilogram.
- In contrast, children weighing more than 10 kg may receive the solution with ½ NS (77 mEq/L).
- These guidelines are for any child who is dehydrated but not have any disease with electrolyte disturbances (e.g. renal failure).
- Children with renal failure may have hyperkalemia or unable to excrete potassium and may not tolerate 20 mEq/L of KCl.
- So, in such conditions, it may be necessary to adjust the electrolyte composition and rate of maintenance fluids.

DEHYDRATION AND REPLACEMENT THERAPY

CASE

A 5-month-old boy presents with copious ***vomiting*** and ***watery diarrhea*** for the last 12 hours. He is not tolerating formula and has not urinated all day. His temperature is 37ºC, pulse 170/minute, respiratory rate 34/minute, and blood pressure 80/42 mmHg. On examination, he is difficult to arouse, his ***eyes are sunken***, his mucous membranes are dry, and his ***anterior fontanel*** is ***depressed***. On skin examination, his capillary refill time is 5 seconds, and he has ***abnormal skin turgor***. Upon stimulation he begins to cry, but he does not produce any tears.

- Dehydration in the pediatric patient is usually secondary to vomiting or diarrhea.
- Neonates and infants are particularly susceptible because of the limited ability of the immature kidney to conserve water and electrolytes and because of the child's dependence on caretakers to meet their needs.

Replacement therapy

- Main sources of normal water loss are (60%), insensible losses from the skin and lungs (35%), and stool (5%).
- Skin water losses due to evaporation are increased in premature infants and neonates who are under radiant warmers or undergoing phototherapy.

- Burns (depending on the severity) can cause a massive loss of water and electrolytes.
- Fever, tachypnea, and tracheostomy increases water losses from the lungs.
- A child who has large amounts of gastrointestinal losses should have these losses measured and replaced with an appropriate replacement solution.
- Urine output is the main measure of water loss.
- Decreased urine output is observed in renal failure and the syndrome of inappropriate antidiuretic hormone (SIADH). Maintenance fluids in a patient with oliguria or anuria produce fluid overload.
- Increased urine output is observed in polyuric phase of acute tubular necrosis, diabetes mellitus, and diabetes insipidus. In such conditions, maintenance fluids are given in excessive amount to prevent dehydration.
- A child with oliguria needs a urine replacement solution.
- A child with polyuria (except for diabetes mellitus) needs insensible loss fluids plus urine replacement.
- Third space losses (edema or ascites) and chest tube output are isotonic and usually require replacement with an isotonic fluid, such as normal saline or Ringer's lactate adjusted according to the child's intravascular volume status.

Dehydration or deficit therapy

- A careful history helps to clarify the differential and provides information concerning the acuity, source, and quantity of fluid lost.
- Recent weight loss and decreased urine output are important indicators of the degree of deficiency.
- Many chronic medical illnesses may present acutely with dehydration (e.g. diabetes, metabolic disorders, cystic fibrosis, and congenital adrenal hyperplasia)
- Polyuria in the presence of physical signs of dehydration may indicate diabetes mellitus, diabetes insipidus, or renal tubular acidosis.
- A child's primary mechanism of compensating for decreased plasma volume is tachycardia; hypotension is a very late and serious finding.
- Serum electrolyte levels help guide the choice of fluid composition and rate of replacement.
- Dehydration may be isotonic, hypotonic (hyponatremic), or hypertonic (hypernatremic), depending on the nature of the fluid lost and the replacement fluids provided by the caretaker.
- **Isotonic dehydration** is the most common form and suggests that either compensation has occurred or that water losses roughly parallel sodium losses.
- **Hypotonic (hyponatremic) dehydration** is defined by serum sodium less than 130 mEq/L. Children who lose electrolytes in their stool and are supplemented with free water or very dilute juices may present with hyponatremic dehydration. The initial goal in treating hyponatremia is correction of intravascular volume depletion with isotonic fluid (normal saline or Ringer's lactate).
- **Hypertonic (hypernatremic) dehydration** (Na ≥150 mEq/L) shows an excessive loss of free water compared with electrolyte loss (e.g. diabetes insipidus). Five percent dextrose (D5) with ½ NS is usually an appropriate starting solution for a patient with hypernatremic dehydration.
- Dehydration, most often due to gastroenteritis, is common in children.
- A patient with **mild dehydration** has few clinical signs or symptoms.
- A patient with **moderate dehydration** has demonstrable physical signs and symptoms.
- A patient with **severe dehydration** is seriously ill. The decrease in blood pressure indicates that vital organs may be receiving inadequate perfusion (shock). Such a patient should receive immediate and aggressive intravenous (IV) therapy.

Fluid management of dehydration in brief

- Restore intravascular volume:
- Normal saline: 20 ml/kg over 20 minutes.
- Repeat as needed
- Calculate 24 hours fluid needs: maintenance fluid+ deficit volume
- Subtract isotonic fluid already administered from 24 hours fluid needs.
- Administer remaining volume over 24 hours using 5% dextrose 1/5 NS + 20 mEq/L KCl.
- Replace ongoing losses as they occur.
- Further details and calculations for rehydration of a child are given in topic about acute diarrhea (in chapter infectious diseases).

SODIUM DISORDERS

HYPONATREMIA

CASE

A 7-month-old girl presents with ***generalized tonic clonic convulsion***. There is history of upper respiratory tract infection. She took only 90 ml milk but 1200 ml free water the day before admission. Neurological examination shows ***bulging anteriorfontanel*** and brisk limbs reflexes. Physical examination of other systems is unremarkable. Brain CT scan is normal. Blood test shows ***sodium level 116 mEq/L***.

- Hyponatremia (serum sodium level less than 130 mEq/L) may occur in the face of decreased, normal, or increased total body sodium content.
- Causes of hypovolemic hyponatremia are:
  - Gastrointestinal (emesis, diarrhea)
  - Skin (sweating or burns)

  - Third space losses (bowel obstruction, peritonitis, sepsis)
- Causes of euvolemichyponatremia are:
  - Syndrome of inappropriate antidiuretic hormone secretion
  - Hypothyroidism
  - Water intoxication
  - Feeding infants excessive water products
  - Diluted formula
- Causes of hypervolemichyponatremia are:
  - Heart failure
  - Cirrhosis
  - Nephrotic syndrome
  - Acute or chronic renal failure
  - Capillary leak caused by sepsis
  - Hypoalbuminemia caused by gastrointestinal disease (proteinlosingenteropathy)
- In children, the most common setting is dehydration.

Clinical findings

- Hyponatremia causes a decrease in the osmolality of the extracellular space.
- Water moves from the extracellular space to the intracellular space to maintain osmotic equilibrium (because the intracellular space has a higher osmolality).
- Due to increase in intracellular water, there is swelling of the cells. Brain cell swelling may cause brainstem herniation and apnea.
- Main symptoms of hyponatremia are anorexia, nausea, vomiting, malaise, lethargy, confusion, agitation, headache, seizures, coma, decreased reflexes, Cheyne-Stokes respirations, muscle cramps and weakness, and rhabdomyolysis.

Diagnosis

- A detailed history may help to know the likely cause of hyponatremia.
- Most children with hyponatremia have a history of volume depletion (diarrhea or diuretic use).
- A history of polyuria is present in primary kidney diseases.
- Brain injury raises the possibility of SIADH.
- The laboratory workup of hyponatremia includes serum electrolytes, glucose, blood urea nitrogen and creatinine, serum osmolality, liver function tests, protein, and lipid levels.
- Urine sodium (UNa) and specific gravity (USG) also assist in diagnosis. In the patient with hypervolemichyponatremia, the urine sodium concentration is a helpful parameter. It is usually <10 mEq/L, except in the patient with renal failure.

Management

- Fluid restriction or replacement
  - Hypervolemic and euvolemichyponatremia usually result from hemodilution. Fluid restriction is the initial treatment in stable, asymptomatic patients. Inhibition of water re-absorption caused by SIADH can be treated on an inpatient basis using vasopressin antagonists or diuretics (furosemide).
  - Hypovolemic hyponatremia can usually be treated with isotonic saline.
- **Sodium replacement:** Sodium deficits can be calculated as follows:
- Na^+ deficit (mEq) = 0.6 × (wt kg) × (140 – serum Na^+)
- If the hyponatremia is acute, is severe (i.e. the serum sodium level is less than 120 mEq/L), and results in CNS symptoms, administration of 3%(hypertonic) saline solution is indicated.
  - The serum sodium concentration should not increase at a rate that exceeds 2 mEq/hour.
  - Hypertonic saline should be discontinued when sodium levels increase to 120 mEq/L or when the patient shows significant clinical improvement.
  - In patients with chronic severe hyponatremia, the rate of serum sodium correction should not exceed 0.5 mEq/L/hour (12 mEq/L/day).
  - Correcting the sodium deficiency too quickly could cause central pontinemyelinolysis.

HYPERNATREMIA

CASE

A 2-month-old infant presents with excessive crying. Mother is giving ***concentrated formula milk***. There is decreased urine output and delayed stooling. On examination, baby is dehydrated. ***Serum sodium*** is ***152 mEq/L***.

- Hypernatremia is a sodium concentration >145 mEq/L.

Causes

- Reduced water intake can be caused by a defective thirst mechanism, unconsciousness, an inability to drink, or a lack of access to water.
- Increased water loss can be caused by vomiting, diarrhea, sweating, fever, hyperventilation, diabetes insipidus, osmotic diuresis, thyrotoxicosis, and severe burns.
- Increased sodium intake or renal salt retention is due to hypertonic saline ingestion or infusion, sodium bicarbonate administration, hyperaldosteronism, Cushing's disease, and congenital adrenal hyperplasia.

Clinical findings

- Most children with hypernatremia are dehydrated. There are typical clinical signs and symptoms of dehydration.
- Patients are irritable, restless, weak, and lethargic. Some infants have a high-pitched cry and hyperpnea.
- Hypocalcemia, which is frequently seen in patients with hypernatremia, may contribute to the neurologic symptoms.
- Physical examination may show orthostatic hypotension, tachycardia, poor skin turgor, dry

mucous membranes, tonic spasms, and respiratory paralysis.

Diagnosis

- The etiology of hypernatremia is usually apparent from the history.
- Laboratory studiesshould include a Complete Blood Count (CBC), serum electrolytes, serum glucose, BUN, creatinine levels and urinalysis (to determine the urine sodium level and osmolality).

Management

- Because of the associated dangers (seizures or coma), hypernatremia should not be corrected rapidly. The goal is to decrease the serum sodium by <12 mEq/L every 24 hours, a rate of 0.5 mEq/L/hour.
- Fluid replacement. The amount of water needed to correct hypernatremia can be estimated as follows:
- Water deficit = body weight × 0.6 (135–145)/[current sodium])
- This calculation is equivalent to 3–4 ml of water per kg for each 1 mEq that the current sodium level exceeds 145 mEq.
- When dehydration is severe, normal saline or lactated Ringer's solution should be administered to improve blood pressure and tissue perfusion.
- Once perfusion is reestablished, 0.45% saline is administered to maintain a urine output of 0.5 ml/kg/hour.
- It is important to address the underlying cause of the hypernatremia, if possible.

POTASSIUM DISORDERS

HYPOKALEMIA

CASE

A 3-month-old infant presents with ***vomiting***, diarrhea and lethargy for 12 hours. On examination, he is dehydrated and ***hypotonic***. On investigation, serum sodium is 135 mEq/L and serum potassium is 1.8 mEq/L ***(hypokalemia)***.

- Hypokalemia, the most common electrolyte abnormality, is defined as a serum potassium level that is less than 3.5 mEq/L.

Causes

- Extra-renal causes include inadequate dietary intake, diarrhea, vomiting, and redistribution (e.g. as a result of insulin administration, epinephrine infusion, or acute alkalemia).
- Drug-induced renal losses are caused by loop diuretics, penicillin, aminoglycosides, and amphotericin B.
- Renal tubular acidosis, Bartter's syndrome, or chronic magnesium depletion can also lead to hypokalemia.

Clinical findings

- Symptoms include weakness, paresthesias, and polyuria.
- Physical examination findings include areflexia, orthostatic hypotension, ileus, paralysis, and arrhythmias.

Diagnosis

- Laboratory studies should include a serum electrolytes, serum BUN, creatinine, creatinine phosphokinase, phosphate, magnesium, and glucose levels, and urinalysis.
- Urinalysis may reveal myoglobin, consistent with rhabdomyolysis.
- Electrocardiography. ECG findings include T-wave flattening or inversion, U waves, and ST segment depression.

Management

- Because of the risk of hyperkalemia, intravenous potassium should be used very cautiously. Oral potassium is safer.
- Oral dose: 2–4 mEq/kg/day with a maximum of 120–240 mEq/day in divided doses.
- The dose of intravenous potassium is 0.5–1.0 mEq/kg, usually given over 1 hour. The adult maximum dose is 40 mEq.
- No more than 40 mEq of potassium should ever be put in a single liter of intravenous fluid and no more than 10 mEq should be given per hour.
- Continuous cardiac monitoring is required.
- Supplementation is more cautious if renal function is decreased because of the kidney's limited ability to excrete excessive potassium.

HYPERKALEMIA

CASE

A 9 months old male infant presents with ***failure to thrive***, poor eating, increased sleeping and irritability for last 3 months. There is family history of polycystic kidney disease. His blood pressure was 102/74 mmHg, heart rate was 162 beats/minute, and respiratory rate was 52 breaths/minute (***acidotic breathing***). On investigation, serum sodium is 121 mEq/L, serum potassium level is 7.1 mEq/L (***hyperkalemia due to renal failure***).

- Normal serum potassium values range from 3.5–5.0 mEq/L. A measurement of 5.5 mEq/L or greater is considered hyperkalemia.

Causes

- Acidosis
- Severe dehydration
- Potassium-sparing diuretics
- Excessive parenteral infusion
- Renal failure

- Adrenal corticoid deficiency (i.e. Addison's disease).
- Renal tubular acidosis
- Massive crush injury
- Beta-blocker or theophylline intoxication

Clinical findings

- Symptomsmay include weakness, paresthesias, and confusion.
- Physical examination findingsmay include paralysis, areflexia, ileus, respiratory insufficiency, or cardiac arrest.

Diagnosis

- Laboratory studies include serum electrolytes, serum BUN, creatinine, glucose, and magnesium levels.
- If the potassium level is extremely high or if the sample was hemolyzed, it is advisable to check another blood sample.
- Electrocardiography. The patient should be placed on a continuous cardiac monitor, and an ECG should be obtained. Peak T waves are the first sign of hyperkalemia followed by a prolonged PR interval and, when most severe, a prolonged QRS complex. Life threatening ventricular arrhythmias may also develop.

Management

- High serum potassium levels and the presence of ECG changes require vigorous treatment.
- Stop all sources of additional potassium (oral, intravenous).
- There are several approaches to acutely lowering potassium levels.
- Calcium chloride or calcium gluconatesolution is administered over 2 minutes and repeated in 5–10 minutes if necessary. This approach, which works by stabilizing cell membranes without altering potassium levels, is the most rapid way of lowering potassium. CaCl should ideally be infused through a central line as it causes severe skin injury if accidentally infiltrated from peripheral IV lines.
- Sodium bicarbonate administered intravenously over 5 minutes and repeated 10–15 minutes later if necessary causes an intracellular influx of potassium. Onset of action occurs in approximately 15 minutes.
- Regular insulin with 10% dextrose administered over 1 hour will lower potassium by causing an intracellular shift. Effects occur 30–60 minutes after administration.
- Furosemide, and acetazolamide all increase potassium excretion.
- Sodium polystyrene sulfonate (Kayexalate) administered orally every 2–4 hours, or as a retention enema every 2–6 hours) causes a sodium–potassium exchange in the colon.
- Dialysis should be considered for patients with severe hyperkalemia who have failed to respond to pharmacologic attempts at lowering the potassium level, and for patients with acute or chronic renal failure.

ACID-BASE DISORDERS

- Acid-base balance refers to the maintenance of blood hydrogen ion concentration.
- pH, is usually closely maintained between 7.35 and 7.45.
- **Acidemia:** A pH below normal (<7.35).
- **Alkalemia:** A pH above normal (>7.45).
- **Acidosis:** A pathologic process that causes an increase in the hydrogen ion concentration.
- **Alkalosis:** A pathologic process that causes a decrease in the hydrogen ion concentration.
- During a metabolic disorder, there is respiratory compensation; the PCO$_2$ decreases during a metabolic acidosis and increases during a metabolic alkalosis.
- During a respiratory process, there is metabolic compensation mediated by the kidneys.
- The kidneys respond to a respiratory acidosis by increasing hydrogen ion excretion, increasing bicarbonate generation, and raising the serum bicarbonate concentration.
- The kidneys increase bicarbonate excretion to compensate for a respiratory alkalosis; the serum bicarbonate concentration decreases.

Table 7.2: Normal values of arterial blood gases.

pH	7.35–7.45
[HCO$_3^-$]	20–28 mEq/L
PCO$_2$	35–45 mmHg

RESPIRATORY ACIDOSIS

CASE

A 9-year-old child presents with Guillain-Barre syndrome. He has developed ***hypoventilation***. Arterial blood gases show a ***low arterial pH*** (<7.36), ***an elevation*** in the ***PCO$_2$*** (hypercapnia) and a compensatory increase in the plasma bicarbonate.

- *Respiratory acidosis* is characterized by a blood carbon dioxide tension (PCO$_2$) greater than 40 mmHg and a decreased blood pH.
- It is associated with inadequate elimination of carbon dioxide by the lungs.

Causes

- Causesof respiratory acidosis include all disorders that reduce pulmonary function and carbon dioxide clearance:
  - CNS lesions
  - Sedative therapy and overdose
  - Neuromuscular disorders (e.g. kyphoscoliosis, scleroderma, flail chest, rib fractures)
  - Pleural disease

  - Obstructive airway disease (e.g. asthma, chronic obstructive pulmonary disease)

Clinical findings

- Respiratory acidosis may lead to symptoms of generalized CNS depression, reduced cardiac output, and pulmonary hypertension.

Diagnosis

- Laboratory studiesshould include an arterial blood gas (ABG) report, serum electrolytes, BUN, creatinine, and glucose levels.
- It may be useful to obtain urine drug screen results.
- Electrocardiography and radiography may be useful.

Management

- Correction of the underlying causeshould be attempted. For example, in the case of drug induced hypoventilation, vigorous attempts should be made to clear the offending agent from the body.
- Assisted ventilation.A PCO_2 of more than 60 mmHg may be an indication for assisted ventilation if CNS or pulmonary muscular depression is severe.

RESPIRATORY ALKALOSIS

> **CASE**
>
> A 10-year-old child has a history of poorly controlled asthma. He presents with worsening shortness of breath. On examination, he is in moderate ***respiratory distress***. Arterial blood gases show pH of 7.54 ***(increased)***, PO_2 of 60 mmHg and a ***PCO_2*** of 29 mmHg ***(decreased)***.

- Respiratory alkalosis is characterized by a decreased PCO_2 and an increased pH.
- It is associated with excessive elimination of carbon dioxide by the lungs.

Causes

- Anxiety is the most common cause of respiratory alkalosis.
- Hypoxia results in an increased respiratory rate and, thus, respiratory alkalosis.
- Primary pulmonary disorders (e.g. pneumonia, asthma, pulmonary fibrosis, pulmonary embolism) lead to stimulation of the ventilatory rate, resulting in a low PCO_2.
- Salicylate toxicity initially causes overstimulation of the respiratory center, resulting in respiratory alkalosis.
- CNS disorders (e.g. cerebrovascular accident, tumor, infection, and trauma) may be associated with inappropriate stimulation of ventilation.
- Early Gram-negative septicemiaresults in a respiratory alkalosis.

Clinical findings

- Acute alkalemia results in a generalized feeling of anxiety, severe obtundation, a tetany-like syndrome, and depressed cardiac function at a blood pH exceeding 7.73.

Diagnosis

- Tests are directed toward finding the underlying cause.
- Some basic tests include an ABG, a CBC, serum electrolytes, serum BUN and creatinine levels, liver studies, a salicylate level, a blood culture, and a chest radiograph.

Management

- The primary goal of therapy is to correct the underlying cause.
- Most cases of respiratory alkalosis require no direct treatment.

METABOLIC ACIDOSIS

> **CASE**
>
> **Diabetic ketoacidosis:** A 12-year-old insulin dependent diabetic child presents with a history of polyuria and thirst. He is febrile, lethargic and dehydrated with ***Kussmaul'srespiration***. Arterial blood gases show ***pH*** 7.26 (decreased), PCO_2 16 mmHg, PO_2 128 mmHg and ***HCO_3*** 7.1 mEq/L ***(decreased)***.

- Metabolic acidosis is defined by a decreased blood pH and a decreased plasma bicarbonate concentration (less than 24 mEq/L).

Causes

- Metabolic acidosis is caused by the loss of bicarbonate or the accumulation of an acid other than carbonic acid (e.g. lactic acid).
- Diarrhea, the most common cause of metabolic acidosis in children, causes a loss of bicarbonate from the body.
- Many inborn errors of metabolism cause a metabolic acidosis. The metabolic acidosis may be the result of excessive production of keto acids, lactic acid, and/or other organic anions.
- Lactic acidosis results from decreased oxygen delivery to tissues and is caused by conditions such as sepsis and shock.
- Ketoacidosis is a condition characterized by increased ketone body formation that occurs as a complication of diabetes mellitus and prolonged starvation.
- Renal failureleads to metabolic acidosis due to the accumulation of various organic and inorganic anions associated with a reduced Glomerular Filtration Rate (GFR).

Anion gap

The difference between the sums of the measured cations ($Na^+ + K^+$) and anions ($Cl^- + HCO_3^-$), termed the anion gap, is normally 12 ± 4.

Table 7.3: Causes of metabolic acidosis.

Increased Anion Gap
Hypokalemia
Hypocalcemia
Hypomagnesemia
Hyperphosphatemia
Diarrheal dehydration
Lactic acidosis
Diabetic ketoacidosis
Salicylate poisoning
Renal failure
Methanol poisoning
Uremia
Normal Anion Gap
Hypernatremic dehydration
Renal tubular acidosis
Hyperalimentation
Decreased Anion Gap
Hyperkalemia
Hypercalcemia
Hypermagnesemia
Hypoalbuminemia
lithium poisoning

Clinical findings

- The clinical features of metabolic acidosis are usually related to the underlying disorder.
- pH levels below 7.2 lead to decreased cardiac output, resistance to catecholamines, hypotension, and Kussmaul's respiration (i.e. a rapid, regular, and deep respiratory rate).

Diagnosis

- Laboratory studiesshould include an ABG, a CBC, serum electrolytes, serum creatinine, BUN, glucose level, and urinalysis.
- Hyperglycemia and glucosuria are characteristic of diabetic ketoacidosis.
- Serum lactic acid levels are elevated in lactic acidosis.

Management

- Most types of metabolic acidosis will resolve with correction of the underlying disorder, improved renal perfusion, and acid excretion.
- Metabolic acidosis may be treated with sodium bicarbonatewhen the blood pH is less than 7.2.
- NaHCO3 (sodium bicarbonate) should be used only when acidosis is severe or difficult to correct.
- Complications of bicarbonate administration include hypernatremia, paradoxic cerebrospinal fluid (CSF) acidosis, hypokalemia, hyperosmolality, and the induction of dysrhythmias.

METABOLIC ALKALOSIS

CASE

A 7-year-old boy is taking excessive amount of bicarbonate during the treatment of renal failure. Arterial blood gases show pH >7.45.

- Metabolic alkalosis is characterized by an increased pH and an increased plasma bicarbonate concentration.

Causes

- Increased bicarbonate results from either increased endogenous production with reduced renal excretion or exogenous administration of bicarbonate or another alkali.
- Vomiting or nasogastric suction causes a loss of gastric hydrochloric acid that leads to an increase in plasma bicarbonate.
- Diuretics that cause volume depletion by the sodium deficit reduces the GFR, stimulates proximal tubular reabsorption of bicarbonate, and maintains the metabolic alkalosis.
- Conditions characterized by excessive mineralocorticoid action (e.g. Cushing's disease, hyperaldosteronism, Bartter's syndrome) stimulate hydrogen ion secretion, thereby raising the plasma bicarbonate level.
- Administration of alkali, either as sodium bicarbonate or as organic ions (e.g. lactate, citrate, acetate), results in an increased plasma bicarbonate level.
- Rapid correction of hypercapniain patients with a chronic state of respiratory acidosis leads to a transient state of hyperbicarbonatemia and an elevated pH.

Clinical findings

- Signs and symptoms of metabolic alkalosis are usually dominated by the underlying disease state.

Diagnosis

- Laboratory tests should include an ABG report, serum electrolytes, serum glucose, BUN, and creatinine levels.

Management

- The primary goal of therapy is to correct the underlying cause.
- Frequently, volume expansion with sodium chloride–containing solutions is required.

Notes

CHAPTER 08

Acutely Ill Child

ANAPHYLAXIS

CASE

Ten minutes after receiving an IV infusion of ampicillin, a 12-year-old boy with meningitis develops ***urticaria*** and ***wheezing***. He also develops tachycardia with ***shortness of breath***.

Definition

- Anaphylaxis is an acute, life-threatening systemic reaction caused by an IgE mediated hypersensitivity reaction.
- It is characterized by:
  - Urticaria-angioedema
  - Acute airway obstruction
  - Circulatory collapse

Pathogenesis

- The most common causes are:
  - Drugs (antibiotics)
  - Hymenoptera (bee) stings
  - Food (peanuts, shellfish)
  - Latex products (gloves)
- The route of allergen administration most commonly is parenteral. Ingestion also is common. Inhalation is less common.
- Anaphylaxis occurs within a few minutes to hours after antigen exposure.
- Systemic manifestations are caused by the release of inflammatory mediators from mast cells and basophils.

Clinical findings

- **Skin:** Urticaria, angioedema, flushing, and itching
- **Respiratory**: Nasal congestion, sneezing, rhinorrhea, hoarseness, stridor, dyspnea, bronchospasm, and hypoxia
- **Cardiovascular**: Dizziness, syncope, hypotension, arrhythmia, palpitations, and substernal pain
- **Gastrointestinal:** Nausea, vomiting, diarrhea, dysphagia, and abdominal cramps
- **Neurologic:** Headache, seizures
- **Genitourinary:** Urgency

Differential diagnosis

- Aspiration of foreign body
- Asthma exacerbation
- Hereditary angioedema
- Panic attack
- Septic shock
- Vasovagal syncope

Diagnosis

- Take a careful history to determine the time between onset of symptoms and exposure to the potential precipitating cause.

Management

- There must be immediate therapy.
- Maintain ABC (airway, breathing, circulation).
- Epinephrine (adrenaline): give intramuscular (I/M) 0.01 ml/kg (of 1:1000 solution, maximum dose 0.5 ml). Repeat every 15min if required. A continuous intravenous infusion (0.1–1.0 mcg/kg per minute) may be required if manifestations are prolonged. Do not use subcutaneous adrenaline, as absorption is less reliable.
- For hypotension, put the patient head-down at 30° (Trendelenburg position) and give intravenous (I/V) normal saline (20 ml/kg bolus).
- Oxygen is given by mask.
- Mechanical ventilation may be required.
- Intravenous (I/V) volume expander is required if there is hypotension. Give 0.9% normal saline (20 ml/kg). Give repeat boluses of 10–20 ml/kg until the blood pressure is restored.
- Bronchodilator therapy with salbutamol for bronchospasm is needed. Continuous nebulized (0.5%) salbutamol is given. Secondary therapy with a steroid, aminophylline and an antihistamine may be helpful for prolonged bronchospasm and capillary leak.
- Relief of upper airway obstruction: mild to moderate edema may respond to inhalation of nebulized 1% adrenaline (1 ml per dose diluted to 4 ml), but intubation of the trachea may be required.
- All patients with anaphylaxis should be observed carefully for at least 12 hours. Patient may deteriorate again over the next few hours.
- Antihistamines
- Steroid: Give intravenous bolus methylprednisolone (2 mg/kg). This dose should be followed by IV methylprednisolone 2 mg/kg/day (divided every 6 hours), or oral prednisolone 2 mg/kg (once a day).

Prevention

- Avoidance of known antigens (drugs, food).

SHOCK

- Shock is a complex metabolic state.
- It is characterized by impaired delivery and utilization of oxygen and other substrates by the tissues.

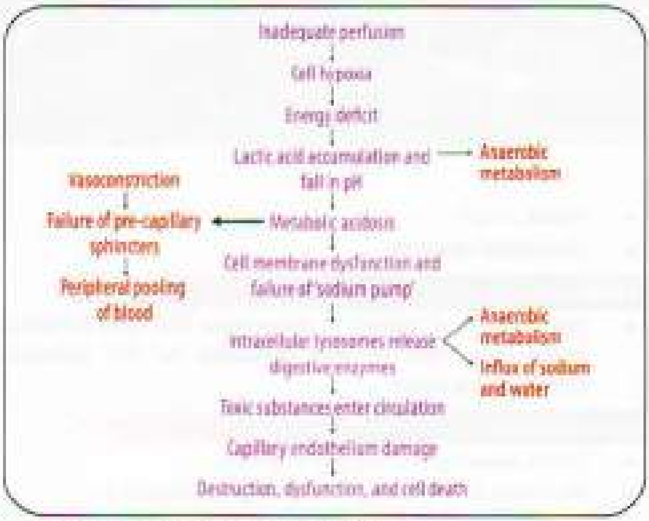

Inadequate perfusion
Cell hypoxia
Energy deficit
Lactic acid accumulation and fall in pH
Anaerobic metabolism
Vasoconstriction
Failure of pre-capillary sphincters
Peripheral pooling of blood
Metabolic acidosis
Cell membrane dysfunction and failure of 'sodium pump'
Intracellular lysosomes release digestive enzymes
Anaerobic metabolism
Influx of sodium and water
Toxic substances enter circulation
Capillary endothelium damage
Destruction, dysfunction, and cell death

Figure 8.1: Pathophysiology of shock.

Cardiovascular causes

- Derangement of preload (hemorrhage)
- Derangement of contractility (myocarditis)
- Derangement of after load (sepsis)

Non-cardiovascular causes

- Hypoxemia
- Hypoglycemia
- Toxins (e.g. cyanide) that impair delivery or utilization of oxygen

Phases of shock

1. **Compensated shock:** Signs of shock with maintained blood pressure
    - Pulse: Tachycardia
    - BP: Normal but postural drop
    - Breathing: Tachypnea
    - Limbs: Cool and mottled
    - CNS: Agitated
    - Laboratory test: Mild metabolic acidosis
2. **Decompensated shock:** Signs of shock [illegible] frank hypotension
    - Pulse: Tachycardia and weak pulses
    - BP: Hypotension
    - Breathing: Tachypnoea and grunting
    - Limbs: Cool, clammy, and pale or blue
    - CNS: Depressed level of consciousness
    - Laboratory test: Metabolic acidosis
3. **Irreversible shock:** Prolonged ischemia [illegible] permanent organ failures
    - Pulse: Tachycardia and weak pulses
    - BP: Hypotension
    - Breathing: Tachypnea and grunting
    - Limbs: Cool, clammy, and pale or blue
    - CNS: Depressed level of consciousness
    - Laboratory test:Metabolic acidosis

Diagnosis

- Complete blood count (to diagnose sepsis)
- Blood gases: Metabolic acidosis (occurs as the result of anaerobic tissue metabolism)
- Electrolytes and urea (to assess dehydration)
- Blood glucose (to exclude hypoglycemia or diabetic ketoacidosis)
- ECG (to evaluate cardiac function)

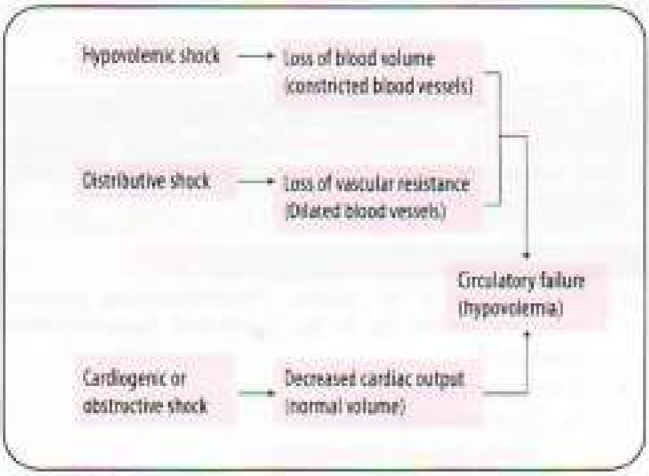

Hypovolemic shock
Loss of blood volume (constricted blood vessels)
Distributive shock
Loss of vascular resistance (Dilated blood vessels)
Circulatory failure (hypovolemia)
Cardiogenic or obstructive shock
Decreased cardiac output (normal volume)

Figure 8.2: Types of shock.

HYPOVOLEMIC SHOCK

CASE

A 14-month-old girl is brought in emergency with complaint of loose motions and vomiting for last two days. On examination her heart rate is 140/minute (*tachycardia*), respiratory rate is 40/minute (*tachypnea*), capillary refill is 3.5 seconds and extremities are cold. There is decreased urine output (*dehydration*).

- Shock is characterized by inadequate systemic perfusion (abnormally low circulating blood volume).
- The causes of hypovolemia are:
    - Trauma
    - GIT bleeding
    - Burns
    - Peritonitis
    - Diarrhea
    - Diabetic ketoacidosis

Diagnosis

- Perform a rapid clinical examination.
- Direct your initial treatment toward the patient's vital signs.

Management

- Follow a standard protocol. Maintain **A**irway, **B**reathing, **C**irculation, and manage **D**isability (ABCD).
- In patients with significant blood loss, blood transfusion will be required (about 20ml/kg to increase hemoglobin concentration by 1 g/dl).
- Patient may need O negative unmatched blood in an emergency.
- Monitor the response with laboratory testing.
- Acutely, blood pressure and perfusion need to be restored with crystalloid infusion.
- Intravenous (I/V) bolus of normal saline, 20 ml/kg, can be given over 15minutes and repeated if necessary.
- In the patient who is dehydrated, the water and electrolyte deficit needs to be replaced.

CARDIOGENIC SHOCK

- It is caused by decreased contractility.
- Cardiogenic shock occurs when the heart is unable to maintain perfusion adequate for the metabolic demands of the tissues.

Pathophysiology

- Same as of hypovolemic shock.

Clinical features

- Tachycardia
- Cool, pale extremities
- Delayed capillary refill
- Impaired mental status
- Pulmonary edema formation
- Hypotension

Management

- Provide supplemental oxygen, FiO_2 100%.
- Intubate if required.
- In shock, elevate the legs to improve venous return. In congestive heart failure elevate the head.
- Secure intravenous (I/V) access. Central access may be required, particularly when using inotropes.
- Control fever with antipyretics (paracetamol 15 mg/kg).
- Correct hypoglycemia and hypocalcemia.
- Acidosis of respiratory cause should be controlled with ventilation.
- For hypovolemia: I/V 20 ml/kg of normal saline is given. In severe volume depletion give 40–60 ml/kg of normal saline.
- Start inotropes when circulation remains unsatisfactory and Chest X-ray (CXR) shows large heart, pulmonary vascular congestion, pulmonary edema, or pleural effusion.
    - Dopamine 1–20 microgram/kg/minute (start at 5microgram/kg/minute).
    - Dobutamine 2–20 microgram/kg/minute (start at 5 microgram/kg/minute).

DISTRIBUTIVE (SEPTICEMIC) SHOCK

- It is caused by disordered perfusion of tissues, often caused by sepsis or toxins.
- Hypotension is due to vasodilatation, (early) leakage of fluid from capillary beds and depression of myocardial contractility.

Clinical findings

- Fever
- Tachycardia
- Low diastolic pressure
- Normal or slightly increased systolic pressure
- Bounding pulses
- Low urine output
- Impaired level of consciousness
- Late signs are similar to those seen in cardiogenic shock

Management

- Correction of triggering derangement (sepsis).
- Collect blood for culture, but do not delay administration of an antibiotic if a blood sample cannot be collected.
- If no information is available regarding the source of pathogen, give ceftriaxone and amikacin.
- For shock due to meningococcemia, which is usually accompanied by a purpuric rash, give cefotaxime 50 mg/kg (max 2 g) I/V 6 hourly. Give benzylpenicillin if cefotaxime not available.
- Maintain circulating blood volume. Treat shock with 0.9% saline solution, 20 ml/kg initially. Further boluses of 10–20 ml/kg may be needed.
- Give oxygen and monitor blood gases. Mechanical ventilation may be required.
- Inotropic support: Commence infusion of an inotropic agent. Dopamine (5–20 mcg/kg per minute) is preferred.
- Defer lumbar puncture, if indicated, until the child has been stabilized.

BURN INJURIES

Burns are a common cause of injury to children.

Types of burns

- **Flame burns** most frequently result from house fires.
- **Scalded burns** occur as a result of burns related to hot water and other liquids.
- **Electrical burns** due to electrocution.
- **Contact burns** due to contact with hot objects such as iron, boilers, and toasters.
- **Chemical burns** are often related to ingestion of caustic agents.
- **Radiation burns** due to sun exposure.

Classification

- Burns are usually classified on the basis of four criteria:

  - Depth of injury
  - Percentage of body surface area involved
  - Location of the burn
  - Association with other injuries

Superficial (first degree) burns

- They are painful, dry, red, and hypersensitive. Sunburn is a common example. Healing occurs with minimal damage to epidermis.

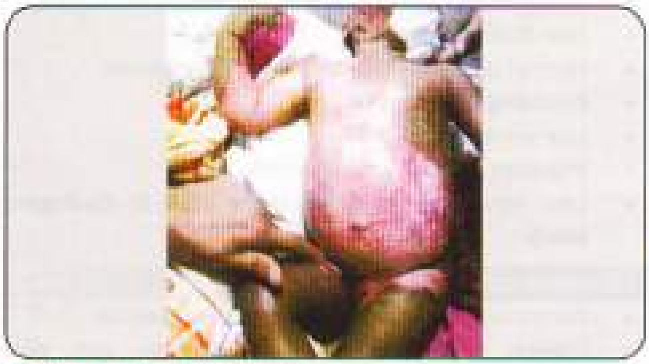


Figure 8.3: First-degree burn.

Partial-thickness (second degree) burns

- These are white and dry, blanch with pressure, and the involved skin has decreased sensitivity to pain.
- They take 3 weeks to heal resulting in scarring.

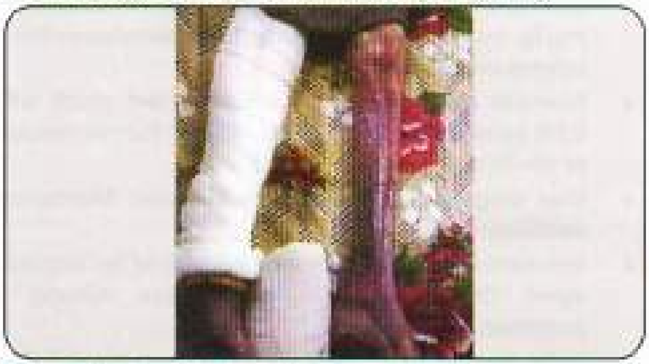


Figure 8.4: Second-degree burn.

Full-thickness (third degree) burns

- Affect all epidermal and dermal elements, leaving avascular skin. The wound is dry, depressed, leathery in appearance, and without sensation. Skin grafting is needed.

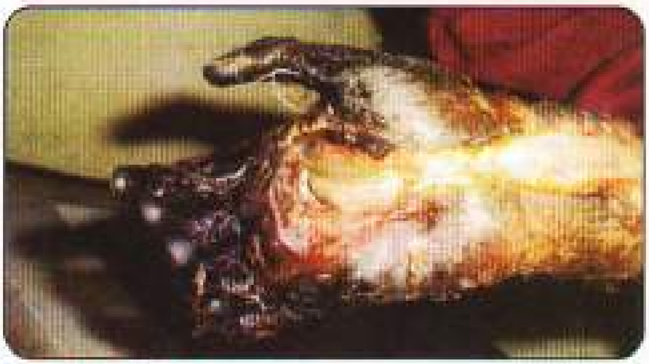


Figure 8.5: Third-degree burn.

Management

First aid measures

- Extinguish flames by rolling on ground or cover the child with blanket.
- Remove clothing saturated with hot liquid.
- Cooling the burn wound—use cold running water 15°C (8–25°C) for 15–20min but avoid making patient hypothermia, cooling must take place as soon as possible
- In case of chemical burn, remove any chemical remaining on the body and wash with water.
- Prevent hypothermia—even without cooling effect of water there is disruption to thermoregulation with a significant burn. Cover burned area with clean, dry sheeting.

Hospital care

- Maintain ABC (airway, breathing, circulation).
- Provide humidified oxygen. Always give 100% oxygen to the patient from a house fire or other enclosed space, even if minor burn.
- Rapid and effective analgesia is given (usually I/V opoids as morphine).
- Treatment of blisters consists of antiseptic cleansing, topical anti-microbial coverage, and observation for infection. Blisters may be debrided (remove devitalized tissue) if needed.
- For deep or extensive burns fluid administration 4 ml/kg per percent of body surface area burned for the first 24 hours, with half in the first 8 hours, in addition to maintenance rates.
- Tetanus prophylaxis: Assess tetanus status in all patients and give booster tetanus toxoid as indicated.

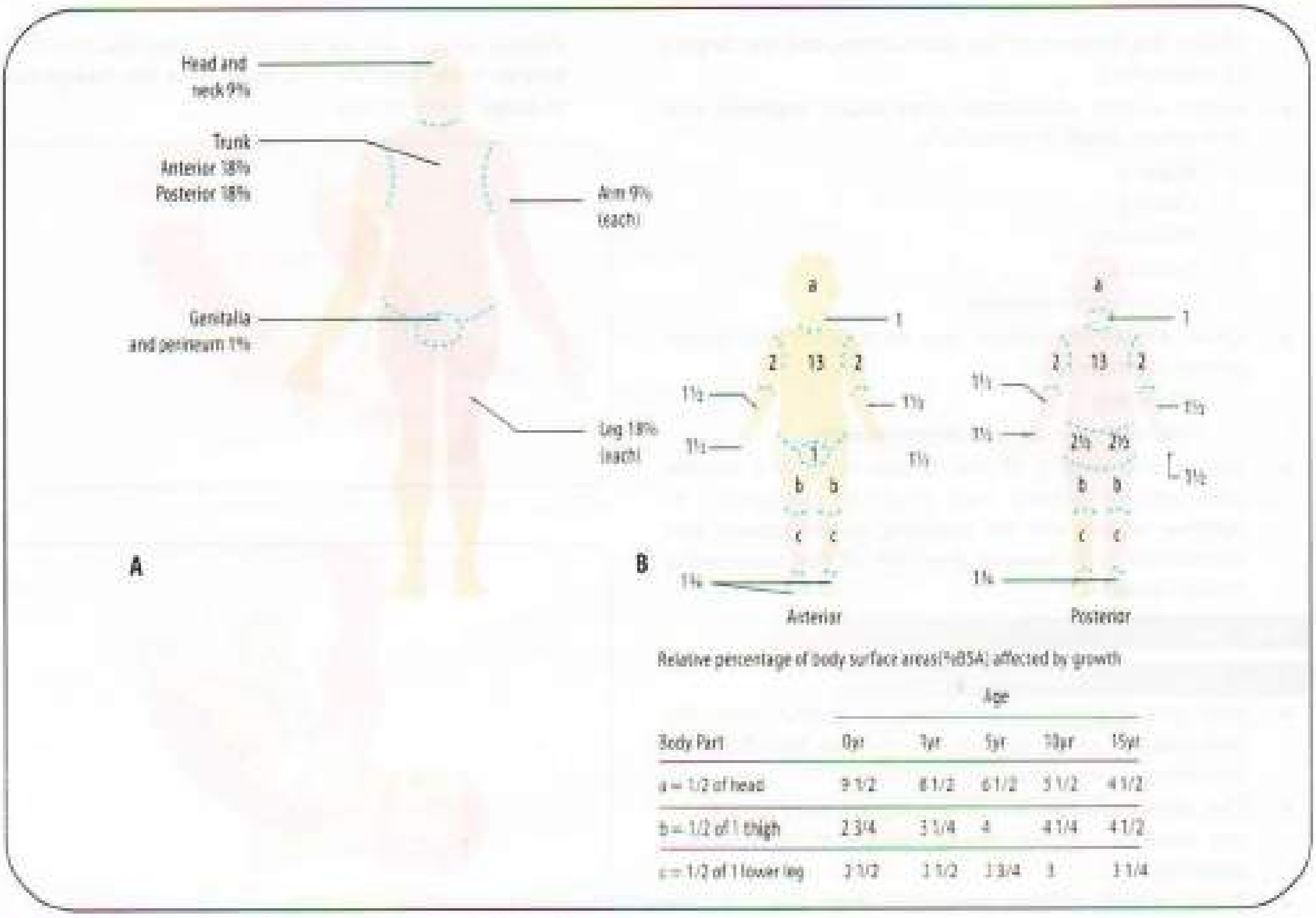
Complications of burns

- Sepsis
- Hypovolemia
- Hypothermia
- Laryngeal edema
- Pulmonary edema
- CO poisoning
- Gastric ulcers
- Contractures

Prevention

- An adult who is drinking a hot liquid should not hold a child.
- Pot handles on the stove should be turned to the side.
- Stable cups and tea making apparatus should be used.
- Children should be in a safe area during food preparation.
- Electric wires should be unplugged from wall sockets after use.
- Electric wires should be inspected for fraying.

Hot appliances should be kept away from children, and vice versa. Ironing should not be performed on the bed or floor.



Relative percentage of body surface areas(%BSA) affected by growth

	Age				
Body Part	0yr	1yr	5yr	10yr	15yr
a = 1/2 of head	9 1/2	8 1/2	6 1/2	5 1/2	4 1/2
b = 1/2 of 1 thigh	2 3/4	3 1/4	4	4 1/4	4 1/2
c = 1/2 of 1 lower leg	2 1/2	2 1/2	2 3/4	3	3 1/4

Figure 8.6: Percentage of body surface area affected by burns.

FOREIGN BODY INHALATION AND CHOKING

CASE

A 3-year-old child, ***previously well***, presents with the ***sudden onset of cough*** and ***wheezing*** while eating nuts. His cough is ***not responding totreatment*** with nebulization. Chest X-ray reveals air trapping ***(hyperinflation) of the left lung with a shift*** of the heart and mediastinum to the right.

- An ingested foreign body is any aspirated substance that is not natural to the body passage in which it is found.
- Foreign body ingestion is a common problem because of :
  - Poor supervision by adults
  - The normal infant behavior of putting things in the mouth or nasal passages
- Children try to run, eat, and breathe at the same time.
- Death from mechanical airway obstruction is most common between 1–4 years of age.
- Food and coins are the most common causes of choking.
- Approximately 50% of aspiration cases are not witnessed by adults.
- Most foreign objects are expelled immediately by the cough reflex and never require medical attention.
- But, foreign body injury is the most common cause of injury-related death in children younger than 1 year of age.
- Factors that influence the severity of the situation include:
  - Size of the foreign body. Large foreign objects may completely occlude the upper airway and must be emergently removed.
  - Location of the foreign body. The younger the child is, the greater the chance that the site of obstruction will be more proximal. The larynx and cricopharyngeus muscle are the most common sites of involvement in children younger than 1 year.

Clinical findings

- A high index of suspicion for foreign body aspiration must be held for any child who presents with unexplained respiratory symptoms.
- The symptoms, physical findings, and complication ratedepend on the nature of the aspirated foreign

object, the location of the obstruction, and the degree of obstruction.

- Upper airway obstruction may cause asphyxia and immediate death. It presents as:
  - Gagging
  - Choking
  - Wheezing
  - Cyanosis
  - Dysphonia or aphonia
- Lower airway obstruction may be tolerated for longer period. It presents as:
  - Wheezing
  - Asymmetric or absent breath sounds
- Edema and lodging of the foreign body in a smaller subsegmental airway may result in obstruction to outflow of air and air trapping or atelectasis and mediastinal shift toward the side of the obstructing foreign body.

Diagnosis

Chest X-ray

- Roentgenographic examination is useful only for radiopaque foreign bodies but may be beneficial for asymmetric lung expansion or collapse.
- The administration of contrast agents may also guide the location of the foreign object if it is in the esophagus.
- If an object causes complete obstruction in the expiratory phase but allows air to pass in the inspiratory phase, air becomes trapped and hyperinflation is seen. This appears as a hyperlucency of the involved side.
- If an object causes complete obstruction in both the expiratory and inspiratory phase, then complete atelectasis occurs with shift of the mediastinum to the side of the obstruction.
- If an object causes incomplete obstruction in both the expiratory and inspiratory phase, a ball-valve effect occurs. This may be revealed in a normal plain radiograph of the chest. However, special inspiratory and expiratory films will reveal air trapping on the affected side.

Bronchoscopy

- Bronchoscopyis usually the only way to definitively diagnose and treat tracheal foreign bodies, although radiographs are helpful for radiopaque objects.

Management

- Object removal:Patients with acute, life-threatening foreign body aspirations should be treated emergently at the scene by either chest blows and thrusts or abdominal thrusts, depending on the age of the patient, while attempting to maintain oxygenation.
- In a child who can cough, breathe, or speak, non-intervention is essential. A natural cough is more effective than airway or chest-compressive maneuvers. Fingers should not be put blindly into the mouth for foreign body removal. This may cause the foreign body to lodge in the airway.

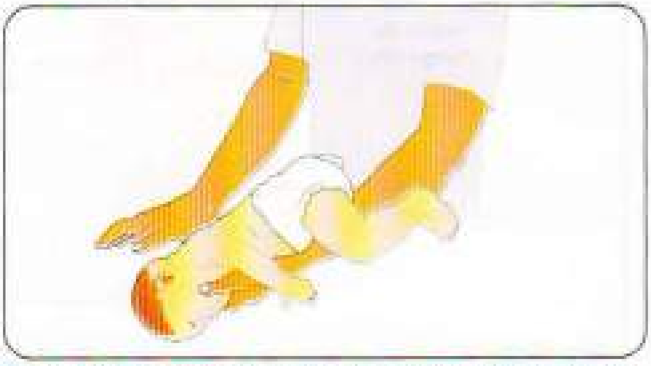


Figure 8.7: Chest thrust method to remove a foreign body.

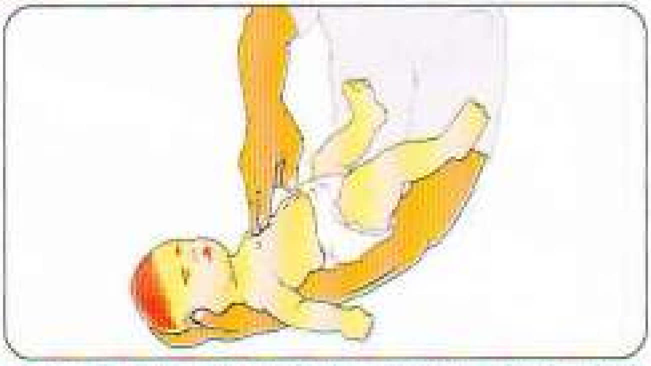


Figure 8.8: Back slap method to remove a foreign body (FB).

- For a child younger than 1 year of age who is unresponsive, back blows and chest thrusts are recommended in concert with attempts at ventilation.
- For an unresponsive child older than 1 year, abdominal thrusts Heimlich maneuver may be performed. Abdominal thrusts are not used for children younger than 1 year of age because of the risk of perforating the abdominal viscus.
- Children in whom abdominal thrusts or chest thrusts fail to dislodge the object may require advanced airway adjuncts to bypass the site of the obstruction until the object can be removed. Airway adjuncts include:
  - Needle cricothyrotomy
  - Surgical cricothyrotomy
  - Rigid bronchoscopy
  - Open bronchotomy
- Endoscopy:Children with more distal foreign bodies should undergo endoscopy.
- Surgery may be necessary to remove the object.
- Antibiotic therapymay be indicated if a secondary infection has developed.

Prevention

- Infants should not be given the toys that can be easily put into mouth.

- Food should be cut, broken, or mashed into bite-sized pieces. Food should not be eaten while playing or running.
- Nuts, hard beans, raw vegetables should not be given to young children.
- Chewable tablets are not recommended for children younger than 3 years of age.
- Children are advised not to put coins in their mouths.

DROWNING (SUBMERSION INJURY)

- Drowning is death resulting from submersion injury within 24 hours of the event.
- Near drowning is a submersion injury in which the person survives for at least 24 hours.
- The peak incidence occurs at 1–5 years of age.
- Bathtub is the most common site of drowning in the first year of life.

Pathophysiology

- Hypoxemia is the main problem in submersion. Aspiration occurs in 90% of cases.
- Hypoxic brain injury is most serious and life threatening. It may cause long-term damage.
- Pulmonary edema is caused by decreased surfactant and resulting atelectasis.
- Acute renal failure occurs in most lengthy drowning and near drowning. Recovery is within 10 days.

Management

- Administer warmed humidified 100% oxygen.
- Monitor continuously core temperature, heart and respiratory rates, and blood pressure.

Table 8.1: Prediction of outcome after submersion.

Prediction of outcome after submersion	
Water temperature	Outcome is better when temperature is greater than 4°C and less than 21°C.
Duration of submersion	Submersion for more than 5 minutes in water >21°C leads to a major risk of damage.
Fixed, dilated pupils and coma	It causes serious deficit, damage, or fatality.
Need for cardiopulmonary resuscitation (CPR)	This leads to poor outcome.

- Consider serum electrolytes, glucose, and arterial blood gases measurements.
- Correct hypoxemia, hypercapnea, glucose and electrolyte disturbances.
- Start slow rewarming.
- Core rewarming with warmed oxygen, continuous bladder lavage with fluid at 40°C, and Intravenous (IV) infusion of isotonic fluids at 40°C is initiated during resuscitation.
- Treat ventricular fibrillation.
- Associated injuries such as neck injury are also treated.

Prevention

- There should be direct supervision for all children younger than 4 years of age while in water.
- Parents should know basic CPR technique.
- School age children should be taught how to swim.

HEAD TRAUMA (INJURY)

- Head injuries may involve the scalp, skull, or underlying brain and blood vessels.
- Injuries may be focal, such as an intracranial bleed, or diffuse.
- Head injury is associated with approximately 50% of trauma deaths, with the mortality rate approaching 35% in patients with severe head injuries.
- In patients with severe head injuries, the Glasgow coma scale and the type of lesion responsible for the neurologic deficits are good indicators of outcome.

Pathophysiology

- Unconsciousness may be induced by either bilateral cerebral cortical injury or injury to the reticular activating system.
- Increased Intracranial Pressure (ICP) results from increased intracranial volume either from a mass (such as a hematoma) or edema, and may be the final result of many different head injuries.
- It can lead to altered level of consciousness, coma, hypertension, bradycardia (Cushing's phenomenon), and death.
- Herniation syndromes can result from focal or diffuse increases in ICP. Cerebellar tonsillar herniation through the foramen causes compression of the medulla with bradycardia, slowing of the respirations, and death.
- Cerebral perfusion pressure derangements. The cerebral perfusion pressure is the mean arterial pressure minus the ICP. Autoregulation of cerebral blood flow may be lost if the ICP remains persistently high.

Clinical findings

- **Concussion** is defined as a transient loss of consciousness or other neurologic function that lasts for a few seconds or minutes (and occasionally longer) and occurs immediately after blunt head trauma. There are typically no permanent sequelae. However, postconcussive syndrome, consisting of headache, decreased memory and attention, insomnia, and dizziness, may persist.
- **Diffuse axonal injury** is secondary to tearing of nerve fibers and is characterized by coma in the absence of a

focal lesion. Autonomic dysfunction (i.e. increased blood pressure, increased temperature, sweating) may be seen.

- **Subarachnoid hemorrhage** is the most common site of bleeding after head trauma. It results in bloody Cerebrospinal Fluid (CSF). The patient may complain of headache and photophobia.
- **Penetrating head injury** is usually obvious in its presentation and is associated with a high mortality rate.

Differential diagnosis

- Causes of altered level of consciousness after head injury that must be ruled out include hypoglycemia, hypoxia, hypotension, hypothermia, alcohol and other drugs, electrolyte abnormalities, and metabolic abnormalities.

Evaluation

- All trauma patients should have their ABCs evaluated initially.
- Pupillary size and reactivity should be evaluated.
- Baseline mental status should be documented.
- The cervical spine must be evaluated for injury in patients with head injury because approximately 10% of patients with severe head injury have an associated cervical spine injury. In an unconscious patient, a hard cervical collar must remain in place.
- The head should be examined, noting the presence of depressed skull fractures, open skull fractures, otorrhea, or rhinorrhea (CSF leaking from the ears or nose).
- The tympanic membranes should be evaluated for hemotympanum, the eyes should be inspected for periorbital hematomas, and the mastoid area should be inspected for ecchymosis, all of which may indicate basilar skull fracture.
- After the initial examination, neurologic assessments should be performed at frequent intervals to search for changes from the initial examination.
- The Glasgow coma scale evaluates the level of consciousness in a quantitative manner, noting eye opening response, verbal response, and best motor response.
- **Vital signs** should be closely assessed, especially noting hypertension in the setting of bradycardia (Cushing's phenomenon).

Diagnosis

- A head CT scan should be performed on patients who have loss of consciousness or altered mental status, abnormal neurologic examination findings, or seizures.
- **Skull radiographs** should be performed on patients with a penetrating head injury or a possible depressed skull fracture (if a head CT scan is not clearly indicated).
- **Laboratory studies** should include an initial glucose level and oxygen saturation level to rule out these factors contributing to altered mental status.
- Other laboratory tests to consider, depending on the degree of injury, include ABG determinations, a serum electrolyte panel, and coagulation studies.

Management

- **Initial stabilization.** The ABCs must be ensured.
- **Fluid resuscitation.** If a patient with a head injury is hypotensive, volume resuscitation must be initiated first. Intravenous fluids must be adequate to maintain blood pressure while avoiding overhydration if increased ICP is suspected.
- **Adequate oxygen and glucose levels must be maintained.**
- **Lowering the ICP.**
  - Hyperventilation:Hyperventilating a patient to a partial pressure of carbon dioxide (PCO_2) of approximately 25–30 mmHg causes cerebral vasoconstriction and helps decrease the ICP.
  - Elevation of the head of the bed.
  - Sedating the patient.
  - Administration of mannitol (20% solution at 1 g/kg) and furosemide.
- **Treatment of seizures.** Seizures are usually treated with phenytoin (1 g infused at 50 mg/minute for adults; approximately 15 mg/kg at 0.5–1 mg/kg/minute, not to exceed 50 mg/minute for children) with or without benzodiazepines.
- **Treatment of scalp wounds.** Scalp wounds should be copiously irrigated. Pressure should be applied to control bleeding (which can be extensive), and the wound should be closed in a single layer with sutures or staples.
- **Emergent neurosurgical consultation** should be sought for patients with lateralizing signs, large focal mass lesions, or any signs of herniation. Evacuation of hematomas, placement of bur holes, or a ventriculostomy may be required. Subarachnoid hemorrhage of traumatic origin does not usually require intervention other than admission for observation.

CHAPTER 09

Neonatology

DEFINITIONS

Neonatal period

- It is defined as first 28 days of life of a live born infant of any gestation.
- It may be further divided into;
    - **Early neonatal period:** First 7 days of life of a live born infant
    - **Late neonatal period:** From day 8 to 28 days of life of a live born infant

Perinatal period

- The period from 28 weeks gestation to 7 days post-natal age

Prenatal period

- The period from 28 weeks gestation to birth

Postnatal period

- The period from birth to 28 days of life

Infant

- First 365 days (1 year) of life

Abortion

- It is expulsion of dead fetus prior to age of viability i.e. 28 weeks gestation in our country and 24 weeks gestation in developed countries.

Still birth

- It is the expulsion of the dead fetus after 28 weeks of gestation.

Perinatal mortality

- Number of stillbirths and early neonatal deaths (up to 7 days of age) per 1000 total births.
- Perinatal mortality rate in Pakistan is 60 per 1000 live births.

Neonatal mortality rate

- Number of deaths in first 28 days per 1000 live births.
- Neonatal mortality rate in Pakistan is 46 per 1000 live births.

Infant mortality rate

- Number of deaths in first 365 days per 1000 live births.
- In Pakistan infant mortality rate is 66 per 1000 live births.

Newborn

- Newborns are classified by:
    - Weight
    - Gestation
    - Weight and gestation

Weight

Low birth weight

- Infant born with less than 2500 gm weight

Very low birth weight

- Infant born with less than 1500 gm weight

Extremely low birth weight

- Infant born with less than 1000 gm weight

Incredibly low birth weight

- Infant born with less than 750 gm weight

Gestation

Preterm

- A baby born less than 37 completed weeks of gestation.

Full term

- A baby born between 37 and 42 weeks of gestation.

Post term

- A baby born more than 42 completed weeks of gestation.

Weight and gestation

Small for gestation (SGA)

- Less than 10th centile in weight expected for gestation.

Appropriate for gestation (AGA)

- Between 10th and 90th centile of weight expected for gestation.

Large for gestational age (LGA)

- More than 90th centile in weight expected for gestation.

HISTORY AND EXAMINATION OF NEWBORN INFANT

Antenatal history

- Maternal age
- Parity (primigravida or grand multipara)
- Any systemic illness before pregnancy like hypertension, diabetes mellitus, nephritis, any heart problem, chronic infection, etc.
- Pregnancy planned or not
- Maternal vaccination for tetanus
- Personal habits like personal hygiene or smoking
- Regular follow up throughout pregnancy or not

Natal history

- Duration of pregnancy
- Amniotic fluid (Oligohydramnios or Polyhydramnios)
- Any passage of meconium stained liquor
- Prolonged rupture of membranes (PROM) for more than 18 hours
- History of labour (prolonged or precipitate)
- Size of placenta
- Umbilical cord (around the neck or ruptured)
- Presentation (vertex, breech, or face)
- Mode of delivery (spontaneous vaginal delivery, forceps, or cesarean section)
- Effect of sedations and anesthesia during delivery

Postnatal history

- Cry at birth (immediate or not).
- Apgar score (1 minute and 5 minutes after birth).
- History of resuscitation at birth.
- Any history of respiratory distress, apnea, severe pallor or jaundice after birth.
- Feeding history after birth.
- Any other illness after birth or admission in neonatal unit.

Past obstetric history

- History of previous pregnancies and deliveries (previous live births, still births, abortions, or problems and mode of deliveries of previous pregnancies).

Family history

- Consanguinity
- History of any neonatal deaths
- History of any congenital anomalies, mental retardation, history of exchange transfusion in other siblings
- Any inborn error of metabolism in other siblings
- History of any acute or chronic illness in family

Socioeconomic history

- Mother and father's income and occupation
- Education of parents
- Housing and living conditions

Examination

- Wash hands properly before examination.
- Room temperature should be appropriate (25–28°C).
- Remove all clothing.
- Take anthropometric measurements (weight, length and head circumference) and plot on growth charts.
- General inspection of the newborn. (Color, activity, posture, any gross congenital anomaly)
- Assessment of gestational age by Ballard score.
- Rapid visual assessment of gestational age.
- Take vitals (respiratory rate, heart rate, temperature, and blood pressure).
    - ○ Normal axillary temperature is 36.5–37.2°C.
    - ○ Normal respiratory rate in a newborn is 40–60 breaths/minute.
    - ○ Normal heart rate is 100–150/minute.
    - ○ Blood pressure correlates directly with gestational and postnatal age of infant and birth weight.
- Examination skin for jaundice, pallor, cyanosis, bruises, rashes, any birth mark or hemangiomas, etc.

Cardio-respiratory system

- Central cyanosis.
- Tachypnea >60/minute.
- Grunting (it is sound produced while expiration against partially closed glottis).
- Sternal and intercostal recessions.
- Peripheral pulses and femoral delay (if femorals are weakly palpable always take four limb blood pressure to rule out coarctation of aorta).
- Listen carefully for cardiac murmurs when baby is quite and calm.
- Listen for breath sounds or any added sounds.

Abdomen

- Look for shape of abdomen (normally full; scaphoid in case of diaphragmatic hernia).
- Check umbilical cord for presence of two arteries and one vein.
- Palpate liver (up to 1–2 cm below costal margin is normal) and spleen (tip of spleen is normally palpable in newborn).
- Palpate both kidneys bimanually.
- Palpate for any other abdominal mass.
- Auscultate for bowel sounds and look for passage of meconium, usually passed within first 48 hours.
- Look for patency and position of anus.
- Look for genitalia (male, female type or ambiguous or undescended testes and any hypospadias, epispadias or meatal stenosis or any evidence of recto-vaginal fistula).
- A large no of newborns pass urine in first 24 hours.

Nervous system

- Posture:
    - ○ Neck retraction.
    - ○ Frog like posture.
    - ○ Hyper extension of limbs.
    - ○ Asymmetrical posture.
- Muscle tone:
    - ○ Increased (hypertonia).
    - ○ Decreased (hypotonia).
    - ○ Tendon jerks.
    - ○ Any abnormal movements (jitters, convulsions).
- Cry:
    - ○ High pitched/shrill. In case of raise intracranial pressure like birth asphyxia
    - ○ Weak and un-sustained, usually in case of serious illnesses and floppy infants

  - Hoarse.
- Trunk and spine:
  - Meningomyelocele
  - Any sacral dimple or pit
  - Any lipoma or tuft of hair at the spine
- Neonatal reflexes:
  - Rooting reflex
  - Sucking reflex
  - Moro reflex
  - Grasp reflex
- Peripheral nerves injuries (Erb's and Klumpke's paralysis).

Head, neck and face

- Dysmorphic features
- Shape and size of the head.
- Shape and size of fontanellae
- Overriding of sutures and premature closure (craniosynostosis)
- Look for scalp veins and texture of hair
- Any evidence of cephal-hematoma, caput succedaneum or craniotabes
- Transillumination for evidence of hydrocephalus.
- Any bruise or edema of face
- Examine shape and position of eyes. Look for any evidence of subconjunctival hemorrhage. Check red reflex in both eyes with ophthalmoscope to rule out cataracts. Look for any abnormal watering and redness of eyes.
- Look for the shape and position of ears, any accessory auricles or pre-aurical pits.
- Check shape and size of nose. Check patency of nostrils.
- Look for shape and size of the tongue. Check for cleft lip/palate, congenital teeth and sucking.
- Look for webbing or abnormally short neck, any cyst, thyroid enlargement or cystic hygroma. Also palpate for sternomastoid tumor and fracture of clavicle.

Limbs and joints

- Look for any fixed deformities like contractures, bands, extra digits and size of all limbs proportionate to trunk and body habitus.
- Especially examine both feet for clubfoot deformity.
- Screen every newborn baby for congenital dislocation of hip joint by performing Barlow and Ortolani maneuvers.

NEONATAL RESUSCITATION

- Neonatal resuscitation at labor room is required to help a newborn to make the respiratory and circulatory transition more effectively and rapidly.
- On average newborn infant gasp after 6 seconds and majority have done so by 20 seconds. With these efforts the lungs rapidly fill with air and residual lung volume is formed.
- Majority of newborns are breathing independently on average of 30–90 seconds. As lungs expands and filled with the air the pulmonary blood flow increases and pressure in left atrium rises closing the foramin ovale. As a consequence, ductus arteriosus closes and independent circulation establishes by cessation of right to left shunting.
- Infants may be asphyxiated in utero or at the time of delivery, so making neonatal transitions difficult requiring resuscitation at birth.
- Human fetuses respond to hypoxia by becoming apneic. When a fetus or infant is deprived of oxygen, an initial period of rapid breathing occurs.
- If the asphyxia continues the respiratory movements cease, the heart rate begins to fall and infant enters a period of apnea known as primary apnea. Exposure to oxygen and stimulation during this period will induce respiration. If asphyxia continues the infant develops deep gasping respiration, heart rate continues to decrease and blood pressure begins to fall. Respiration becomes weaker and irregular and finally infant enters into a period of apnea known as secondary apnea. At this stage positive pressure ventilation is required and there is an increased risk of brain damage. Primary and secondary apneas are clinically indistinguishable at birth, so always assume a secondary apnea at birth and prompt resuscitation should be started immediately.

Preparation for resuscitation

- For prompt and effective resuscitation, two major factors must be given proper attention:
  - Anticipation (the need for resuscitation): Especially if there are antipartum and intrapartum risk factors for birth asphyxia.
  - Adequate preparation (equipment and personnel).
- Preparation:
  - Identify helper
  - Prepare the area for delivery
  - Wash hands
  - Prepare an area for ventilation and check equipment

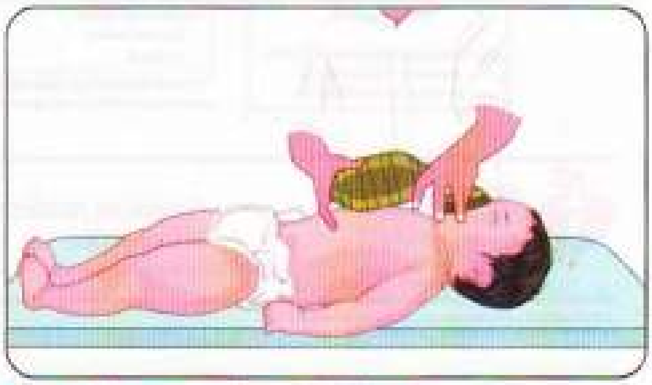
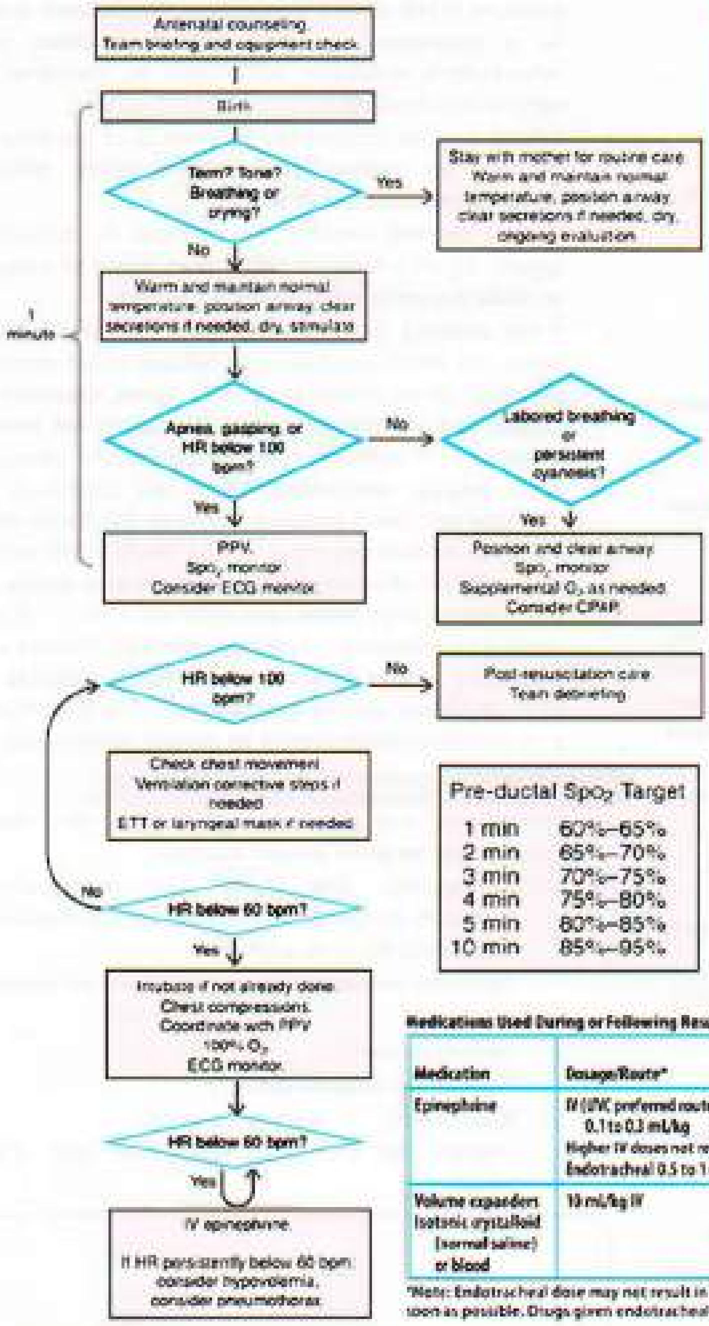


Figure 9.1: Resuscitation with ambu bag.

Neonatal Resuscitation Program® - Reference Chart

The most important and effective action in neonatal resuscitation is ventilation of the baby's lungs.


Antenatal counseling
Team briefing and equipment check
Birth
1 minute
Term? Tone? Breathing or crying?
Yes
Stay with mother for routine care. Warm and maintain normal temperature, position airway, clear secretions if needed, dry, ongoing evaluation
No
Warm and maintain normal temperature, position airway, clear secretions if needed, dry, stimulate
Apnea, gasping, or HR below 100 bpm?
No
Labored breathing or persistent cyanosis?
Yes
Position and clear airway
SpO₂ monitor
Supplemental O₂ as needed
Consider CPAP
Yes
PPV
SpO₂ monitor
Consider ECG monitor
HR below 100 bpm?
No
Post-resuscitation care
Team debriefing
Check chest movement
Ventilation corrective steps if needed
ETT or laryngeal mask if needed
No
HR below 60 bpm?
Yes
Intubate if not already done
Chest compressions
Coordinate with PPV
100% O₂
ECG monitor
HR below 60 bpm?
Yes
IV epinephrine
If HR persistently below 60 bpm:
consider hypovolemia,
consider pneumothorax

Pre-ductal SpO_2 Target

1 min	60%–65%
2 min	65%–70%
3 min	70%–75%
4 min	75%–80%
5 min	80%–85%
10 min	85%–95%

Ⓐ Airway
- Put baby's head in "sniffing" position
- Suction mouth, then nose
- Suction trachea if meconium-stained and NOT vigorous

Ⓑ Breathing
- PPV for apnea, gasping, or pulse <100 bpm
- Ventilate at rate of 40 to 60 breaths/minute
- Listen for rising heart rate, audible breath sounds
- Look for slight chest movement with each breath
- Use CO_2 detector after intubation
- Attach a pulse oximeter

Ⓒ Circulation
- Start compressions if HR is <60 after 30 seconds of effective PPV
- Give (3 compressions: 1 breath) every 2 seconds
- Compress one-third of the anterior-posterior diameter of the chest

Ⓓ Drugs
- Give epinephrine if HR is <60 after 45 to 60 seconds of compressions and ventilation
- Caution: epinephrine dosage is different for ET and IV routes

Corrective Steps

M	Mask adjustment.
R	Reposition airway.
S	Suction mouth and nose.
O	Open mouth.
P	Pressure increase.
A	Airway alternative.

Endotracheal Intubation

Gestational Age (weeks)	Weight (kg)	ET Tube Size (ID, mm)	Depth of Insertion* (cm from upper lip)
<28	<1.0	2.5	6-7
28-34	1.0-2.0	3.0	7-8
34-38	2.0-3.0	3.5	8-9
>38	>3.0	3.5-4.0	9-10

*Depth of insertion (cm) = 6 + weight (in kg)

Medications Used During or Following Resuscitation of the Newborn

Medication	Dosage/Route*	Concentration	Wt (kg)	Total IV Volume (mL)	Precautions
Epinephrine	IV (UVC preferred route) 0.1 to 0.3 mL/kg Higher IV doses not recommended Endotracheal 0.5 to 1 mL/kg	1:10,000	1 2 3 4	0.1-0.3 0.2-0.6 0.3-0.9 0.4-1.2	Give rapidly. Repeat every 3 to 5 minutes if HR <60 with chest compressions.
Volume expanders Isotonic crystalloid (normal saline) or blood	10 mL/kg IV		1 2 3 4	10 20 30 40	Indicated for shock. Give over 5 to 10 minutes. Reassess after each bolus.

*Note: Endotracheal dose may not result in effective plasma concentration of drug, so vascular access should be established as soon as possible. Drugs given endotracheally require higher dosing than when given IV.

American Heart Association
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American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN

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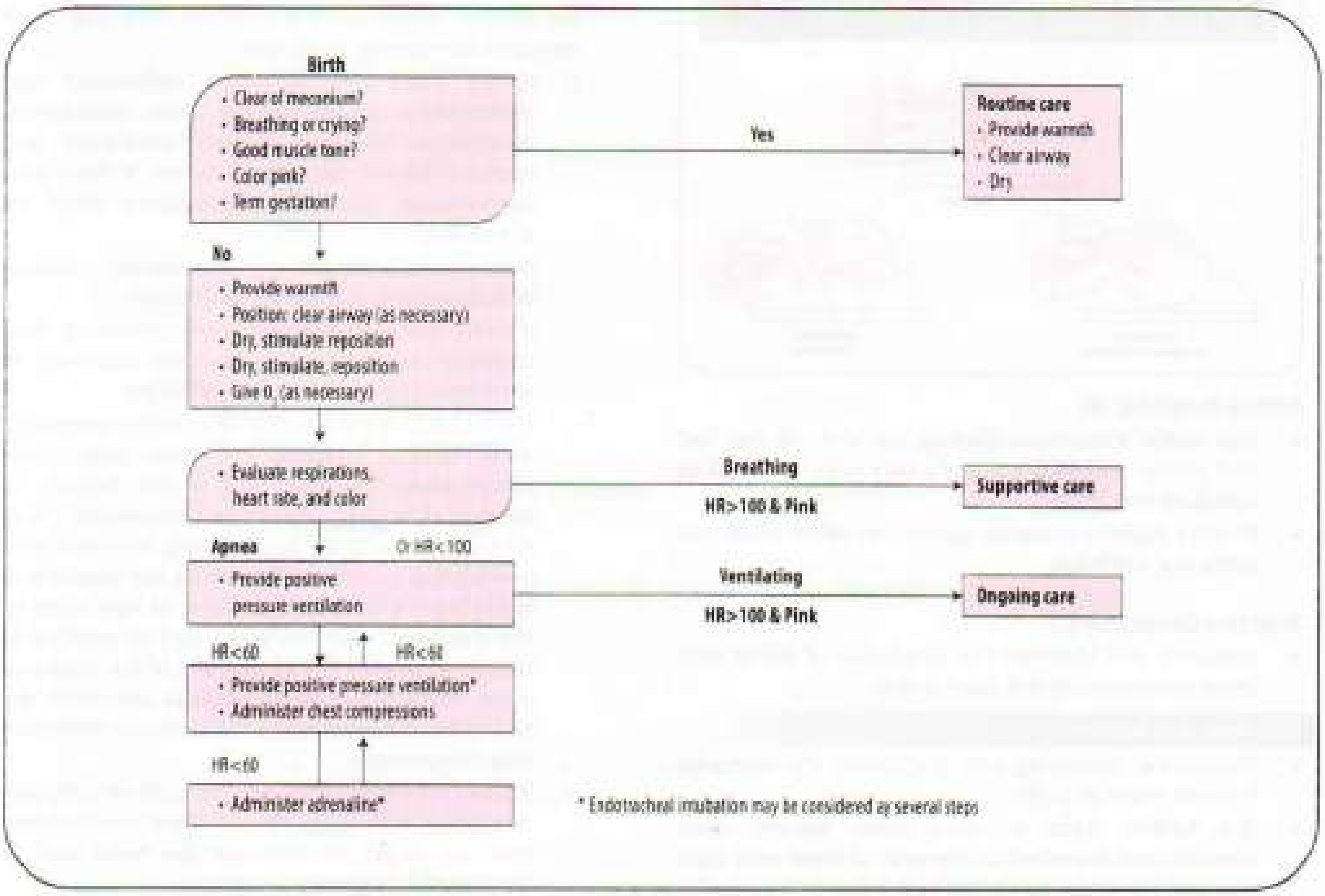
The recommendations in this publication do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

Equipment required

- Resuscitation table
- Sterile linen
- Suction apparatus (suction catheter, rubber/silicon bulb mucous extractor)
- Ambu bag and face masks (newborn and premature sizes)
- Oral air ways (newborn and premature sizes)
- Endotracheal tubes (sizes 2.5, 3.0, 3.5 and 4.0 mm)
- Stylet, scissors, gloves
- Two pieces of cloth (one to dry the baby, one to cover the baby after drying)
- A cap to cover the baby's head
- A clock or stopwatch
- Medications:
  - ○ Epinephrine 1: 10,000
  - ○ Naloxone hydrochloride
  - ○ Sodium bicarbonate 4.2% or 8.4%
  - ○ Dextrose water 10%
  - ○ Sterile water
- Miscellaneous:
  - ○ Radiant warmer
  - ○ Stethoscope
  - ○ Adhesive tape
  - ○ Syringes (1 cc, 3 cc, 5 cc, 10 cc and 20 cc)
  - ○ Butter fly needles 25 G
  - ○ Umbilical artery catheterization tray
  - ○ Umbilical catheter 3 and 5 Fr
  - ○ Feeding tube 5 Fr
  - ○ Spirit sponges


Birth
• Clear of meconium?
• Breathing or crying?
• Good muscle tone?
• Color pink?
• Term gestation?
Yes
Routine care
• Provide warmth
• Clear airway
• Dry
No
• Provide warmth
• Position: clear airway (as necessary)
• Dry, stimulate reposition
• Dry, stimulate, reposition
• Give O_2 (as necessary)
• Evaluate respirations, heart rate, and color
Breathing
HR>100 & Pink
Supportive care
Apnea
Or HR< 100
• Provide positive pressure ventilation
Ventilating
HR>100 & Pink
Ongoing care
HR<60
HR<60
• Provide positive pressure ventilation*
• Administer chest compressions
HR<60
• Administer adrenaline*
* Endotracheal intubation may be considered at several steps

Neonatal resuscitation.

Steps of resuscitation

- A very important aspect of resuscitation is evaluating the infant, deciding what action to take and then taking action.
- The Apgar score is not used in determining when to initiate resuscitation or in making decision regarding the course of resuscitation but the Apgar score is important in assessing the effectiveness of the resuscitative measures.
- Evaluation is primarily based on the following three signs:
  1. Respiration
  2. Heart rate
  3. Color

Initial steps and ABC's of resuscitation are:

Prevent heat loss.

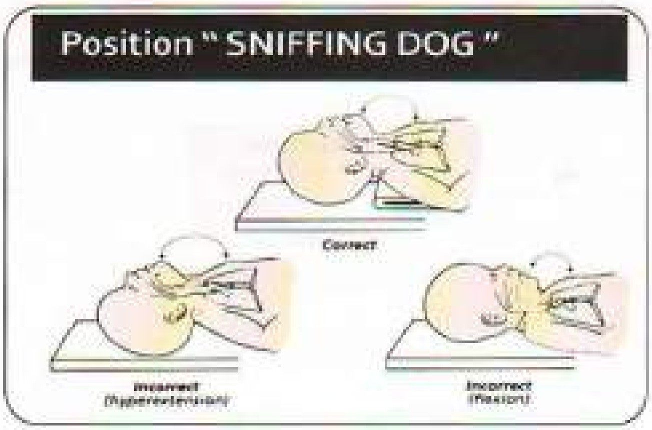
- Dry thoroughly.

Keep resuscitation room temperature above 25 C^0

If baby needs active resuscitation, do it at Radiant warmer If not then place the baby on mother chest to provide warm by kangaroo mother care(KMC)

Open the Airway (A)

- Position the infant slightly extended to help keep the airway open and clear the airway.
- Suction the infant's mouth first and then nose provided that there copious oral secretions, blood , meconium and before ambu bagging. If the baby is having normal breathing , then there is no need to suction in each neoborn.


Position " SNIFFING DOG "

Initiate Breathing (B)

- Use tactile stimulation (flicking the soles of the feet and gently rubbing the infant's back once or twice) to stimulate respiration.
- Employ positive pressure ventilation when necessary using bag and mask

Maintain Circulation (C)

- Stimulate and maintain the circulation of blood with chest compressions and medications.

Decisions and actions

- Positioning, suctioning and stimulation are necessary in every infant at birth.
- The further steps in resuscitation depend upon evaluation of the infant on the basis of three vital signs (Respiratory effort, heart rate and color).

Respiratory effort

- After stimulating the infant, the main question to ask is "Does the infant show the respiratory effort?"
    - Yes! Breathing is there–If there are adequate chest movements, check the heart rate.
    - No! There is no breathing (apnea)–Baby should be given positive pressure ventilation (PPV) using a bag and mask. Ventilation rate should be 40 to 60/minute, and pressure required for initial breaths is 25–30 cm H_2O in term babies and subsequent breaths may be delivered at the pressure of 15–20 cm H_2O. Lower pressure should be used in very low birth babies.
- PPV with endotracheal intubation is indicated in:
    - Ineffective bag and mask ventilation
    - Prolonged PPV required
    - Suspicion of diaphragmatic hernia
    - Preterm infant who will eventually require assisted ventilation
    - Infant who require intubation due to thick meconium
    - Continue ventilation for 40 to 60/ minutes but when done with cardiac compression ventilation rate should be 30/min

Heart rate

- As soon as respiratory effort has been evaluated (and appropriate action taken if needed), next important step is to monitor the heart rate.
    - If the heart rate is above 100/minute and spontaneous respiration has been established, discontinue positive pressure ventilation and evaluate color of the baby. However, if there is no spontaneous respiration, ventilation must be continued.
    - If heart rate is 60–100 and is increasing, continue ventilation until it is above 100/minute.
    - If heart rate is 60–100 and is not increasing, then continue ventilation and check for adequacy of ventilationapply mneumonic MRSOPA
    - If the heart rate is less than 60/minute, even after 30 seconds of effective, PPV then begin chest compression. The lower half of the sternum i.e below nipple level s should be compressed 1/3 of AP diameter of chest by encircling the chest with overlapping thumbs or by placing the middle and index finger of one hand together at right angle to the chest wall over the lower part of sternum in coordination with PPV at the ratio of 3:1. Continue chest compression for 60 seconds and check the heart rate, if it is more than 60/min and increasing stop compression.
    - If heart rate is not improving in spite of adequate ventilation with 100% O_2 and chest compression, then use drugs to stimulate the heart and to increase the tissue perfusion.
- Following drugs are commonly used:
    - Epinephrine: available in 1mg/ml 1:1000) preparation, dilute 10 times it make (1: 10,000) dilution
    - i.e add 9ml of distil water with 1 ml of inj in 10 ml syringe and then draw in 1ml syringe for usage. Indicated when heart rate is not improving in spite of adequate effective ventilation and chest compressions. Dose is 0.1–0.3 ml/kg of (1:10.000) dilution preparation I/V. Dose can be repeated in

MRSOPA

The 6 Ventilation Corrective Steps: MR. SOPA

<table>
<tr><th></th><th>Correction Steps</th><th>Action</th></tr>
<tr><td>M</td><td>Mask adjustment.</td><td>Reapply the mask. Consider the 2-hand technique.</td></tr>
<tr><td>R</td><td>Reposition airway.</td><td>Place head neutral or slightly extended.</td></tr>
<tr><td colspan="3"><i>Try PPV and reassess chest movement.</i></td></tr>
<tr><td>S</td><td>Suction mouth and nose.</td><td>Use a bulb syringe or suction catheter.</td></tr>
<tr><td>O</td><td>Open mouth.</td><td>Open the mouth and lift the jaw forward.</td></tr>
<tr><td colspan="3"><i>Try PPV and reassess chest movement.</i></td></tr>
<tr><td>P</td><td>Pressure increase.</td><td>Increase pressure in 5 to 10 cm H_2O increments, max 40 cm H_2O.</td></tr>
<tr><td colspan="3"><i>Try PPV and reassess chest movement.</i></td></tr>
<tr><td>A</td><td>Alternative Airway</td><td>Place an endotracheal tube or laryngeal mask.</td></tr>
<tr><td colspan="3"><i>Try PPV and assess chest movement and breath sounds.</i></td></tr>
</table>

3–5 min. Or intra-tracheal (less preferable) dose is 0.3 to 1ml/kg of (1:10.000) dilution.

- Volume expanders: (Normal saline or blood). These are indicated where there is evidence or suspicion of hypovolemia e.g. pallor persisting after oxygenation, weak pulses with good heart rate, poor response to resuscitation. Dose is 10 ml/kg I/V in 5–10 min.
- Sodium bicarbonate : Not recommended now a days
- Naloxone hydrochloride: It is indicated when there is H/O maternal narcotic administration within past 4 hours. Dose is 0.1 mg/kg through endotracheal tube, I/V, I/M or S/C.

- Discontinue resuscitation if there is no respiratory activity or heart is inaudible and pupils are dilated and fixed after 10 minutes of effective resuscitation.
- **Resuscitation in meconium stained liquor babies**
- Suction of meconium stained babies is not recommended till complete delivery of baby.
- If there is apnea , or gasping , then first do ambu bagging after oral and nasal suction and if there is no air entry or no improvement with ambu abg then put ETT and first do tracheal suction either through meconium aspirator or suction tube and then give breaths.

CARING A NORMAL NEWBORN INFANT

The main steps for newborn care are:

- Promoting mother–infant bonding
- Establishing feeding (especially breastfeeding)
- Teaching the technique of newborn care
- Place the baby in skin to skin contact with the mother which will keep the baby warm. Promote mother infant bonding as well as help in making early breastfeeding successfully.
- Early breastfeeding is strongly recommended. Indications that the baby is ready for feeding include alertness and vigor, absence of abdominal distention, good bowel sounds, and normal hunger cry. The healthy term newborn should be allowed to feed every 2–5 hours on demand. The first feeding usually occurs by 2–3 hours of life, often as early as in the delivery room.
- Vitamin K (1 mg IM) is given within 2–4 hours after birth.
- Hepatitis B vaccine (0.5 ml) is given to all newborns with birth weight >2000 g. if the mother is HbsAg positive, HBIG(Hepatitis B immunoglobin) is also given but on alternate leg.
- If the mother is type O or Rh–negative blood group, blood grouping and Coombs testing of newborn is done. Rh –ve mother should be given anti-D injection if Rh +ve baby is delivered.
- Infants should be positioned supine or lying on the right side with the dependent arm forward to minimize the risk of aspiration.
- Newborn baby should be nursed in a thermo-neutral environment. The clothing and bedding should be minimal, only those needed for an infant's comfort.
- Proper hand washing to handle the baby and cord care: apply 1% chlorhexidine digluconate gel once daily for 7 days in resource limited countries is important. However for hospital deliveries or deliveries in developed countries clean cord care practices are recommended by WHO.
- Weight, length, and head circumference should be measured.
- Bathing may be delayed until 6to 24 hours. More harm comes from bathing babies in labour room or ward. It is one of the commonest causes of neonatal hypothermia.

TEMPERATURE REGULATION IN NEWBORN INFANT

- Normal skin temperature in the neonate is 36.0–36.5°C (96.8–97.7°F).

- The normal core (rectal) temperature is 36.5–37.5°C (97.7–99.5°F).
- Axillary temperature may be 0.5–1.0°C lower (95.9–98.6°F).
- The chance of survival of neonate is markedly enhanced by the successful prevention of excessive heat loss.
- For this purpose, the newborn infant must be kept under a **neutral thermal environment**. It is defined as the environmental temperature at which heat production and O_2 consumption is minimal yet the core temperature is maintained within normal range.
- Term newborn has brown fat (around scapula) as a source for thermogenesis, which is highly vascularized and innervated by sympathetic neurons. When these infants face cold stress, noradrenaline levels increase and act in the brown-fat tissue to stimulate lipolysis. Most of the free fatty acids (FFA) are re-esterified or oxidized; both reactions produce heat. Hypoxia or beta-adrenergic blockade decreases this response.

HYPOTHERMIA

CASE

A pre-term newborn of 2 kg weight was normal at birth. He presents at 12 hours of age because of not taking feed. He is ***lethargic*** with cyanosed extremities. His ***temperature*** is less than ***96.8°F***.

Definition

- Hypothermia is defined as a core temperature of less than 36°C (96.8°F).

Mechanisms of heat loss

- **Radiation:** Radiation is heat loss from the infant (warm object) to a colder nearby object.
- **Conduction:** Conduction is direct heat loss from the infant to the surface with which he is in direct contact.
- **Convection:** Convection is heat loss from the infant to the surrounding air.
- **Evaporation:** Heat may be lost by water evaporation from the skin of the infant. This especially occurs immediately after delivery.

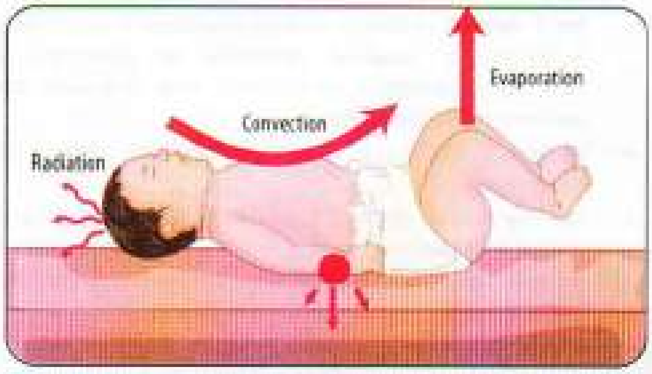


Figure 9.4: Mechanisms of heat loss.

Risk factors

- **Preterm infants** are predisposed to heat loss because they have little subcutaneous fat, a high ratio of surface area to body weight, and reduced glycogen and brown fat stores. They have immature shivering and vasoconstriction mechanisms in response to cold stress. They often require resuscitation, which require exposure for assessment, and this result in cold stress.
- **Intrauterine growth retardation:** They have relatively large surface area to body ratio and lack of subcutaneous fat.
- **Birth asphyxia:** These newborns have poor peripheral circulation and become hypothermic especially if prolonged resuscitation is required.

Clinical findings

- Infant is too cold to touch, has weak sucking and cry and less activity.
- There may be slow, irregular breathing, slow heart rate (bradycardia), cyanosis, sclerema or generalized bleeding (DIC).

Complications of hypothermia

- Hypoglycemia, metabolic acidosis, hypoxia.
- Clotting disorders: DIC and pulmonary hemorrhage.
- Shock, decreased perfusion.
- Intraventricular hemorrhage.
- Apnea, severe sinus bradycardia, increased neonatal mortality.

Management

- Prevention is the best management. Remove precipitating factors where possible.
- In the delivery room dry the infant, especially the head; place the infant under a radiant warmer; place the hat on the head of the infant; do not bath the infant in the delivery room and ensure a temperature 28°C in the delivery room.
- Place high-risk infants in neonatal unit. Check temperature 1 hourly. Check for signs of infection. Ensure a temperature of 25°C in nursery all the times.
- Slow rewarming is indicated in hypothermic neonate. Rewarm at a rate of 0.6–1.0°C/hour. During rewarming, the skin temperature should not be >1.0°C warmer than the coexisting rectal temperature.
- Full term infant can be rewarmed under a radiant warmer, but preterm may require an incubator.
- Investigate and manage for sepsis if the infant previously had normal temperature.

HYPERTHERMIA

CASE

A newborn of 2 days of age presents with poor feeding, dehydration and ***fever***. He is highly irritable. Body ***temperature is 102°F***.

Definition

- Hyperthermia is defined as a temperature, which is greater than the normal core temperature of 37.5°C (99.5°F).

Causes

- Infections
- Dehydration
- Environmental causes (excessive environmental temperature, over-wrapping, etc.)
- Maternal fever during delivery

Complications

- Increased metabolic rate and oxygen consumption
- Tachycardia, tachypnea, irritability
- Periodic breathing, apnea
- Dehydration, acidosis, brain damage, death

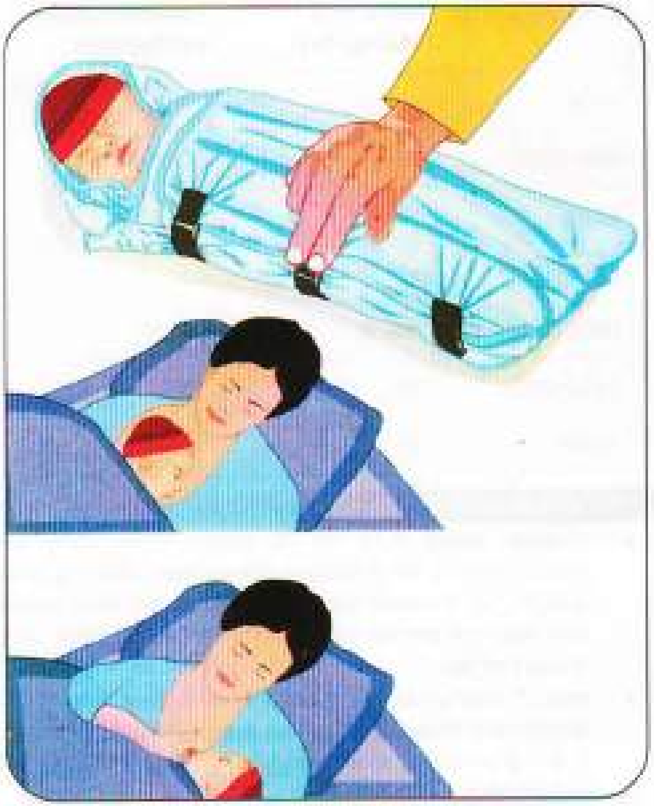


Figure 9.5: Methods to prevent hypothermia.

Management

- Remove and manage the causative factor for hyperthermia. In environmental causes whole body of the infant will be warm, but in true fever due to infection, extremities will be cold secondary to peripheral vasoconstriction.
- Treat infection, if it is apparent clinically and on septic screen.
- Correct dehydration.
- Turn off any heat source and remove excessive clothing.
- Do tepid water sponge bath.
- Paracetamol (5–10 mg/kg/dose, orally or rectally, every 4 hourly).

NUTRITIONAL MANAGEMENT OF THE NEWBORN

- The composition and type of nutritional fluid and the route of administration depends on the gestational age, general medical condition, and possible special nutritional needs of the newborn.
- For preterm as well as full term babies, breast milk is the best and most easily tolerated food.
- **Calories are required:**
    - To maintain weight: give 50–60 Kcal/kg/day
    - To induce weight gain: give 100–120 Kcal/kg/day to a term infant (normal weight gain is 15–30 g/day), and 110–140 Kcal/kg/day to a premature infant (normal weight gain 15 g/day)
- The source of calories comprises of:
    - Carbohydrates 11–15 g/kg/day (30–60% of total calories)
    - Protein 2.25–4.0 g/kg/day (7–16% of total calories)
    - Fat 4–6 g/kg/day (<55% of total calories)

Criteria for initiating infant feeding

- Most healthy term infants are fed within the first 4 hours.
- The following criteria should usually be met before initiating infant feeding.
    - No history of excessive oral secretions, vomiting, or bilious gastric aspirate.
    - Non-distended, soft abdomen, with normal bowel sounds.
    - Clinically stable infant especially preterm.
    - Extubation: At least 6 hours should be allowed to pass after extubation before attempting feeding.
    - Respiratory rate <60 breaths/minute for oral feeding and <80 breaths/minute for NG feeding.

Nutritional considerations

- The term infant should be breast-fed on demand.
- The otherwise healthy preterm infant who is between 34 and 38 weeks gestational age should be fed every 3 hours breast, by bottle, or gavage, depending on the infants' strength and alertness. The fluid for the initial bottle or NG feeding is sterile water. If water is tolerated without aspiration or regurgitation, the infant can be advanced to formula or human milk.
- The preterm infant who is less than 34 weeks gestational age or weight less than 1500mg does not have a well-coordinated suck–and–swallow reflex, and therefore should be fed via a feeding tube. The feeding may be gastric bolus every 2–3 hours.
- **Indications are:**
    - Infants <34 weeks gestational age

  - Preterm infants who lack energy for sucking may require a combination of nipple and gavage feeding
  - Sick infants with impaired suck and swallow mechanism
- With the infant's head placed to the side, pass a 5F or 8F feeding tube through the mouth or nose.
- The distance from the nose to the ear and to the point between xiphoid processes and umbilicus should first be marked on the tube.
- Check tube position by injecting air and auscultating over the stomach. After the tube is placed, residual gastric aspirate is checked, the volume recorded, and the aspirate returned to prevent metabolic complications from continued acid and electrolyte removal.
- A measured amount of fluid is poured into a syringe attached to the tube and allowed to drip in by gravity. Never inject the fluid under pressure.
- When the tube is removed, it is pinched closed to avoid dripping fluid into the pharynx.

Nasogastric feeding guidelines

- Human milk is recommended wherever possible for feeding infants.
- Start trophic feeding by 10–20 ml/kg/day (3 hourly). When tolerated proceed to actual feed with daily increments by 10–20 ml/kg/day (slow feeding) or 20-40ml/kg/day (rapid feeding) till the final feed volume is achieved (160–200 ml/kg/day).
- Once full strength 20cal/oz is tolerated, consider advancing to 24 to 30cal/oz feedings by adding human milk fortifiers.

Weight 1500–2000 g

- Breast milk or term infant formula can be given.

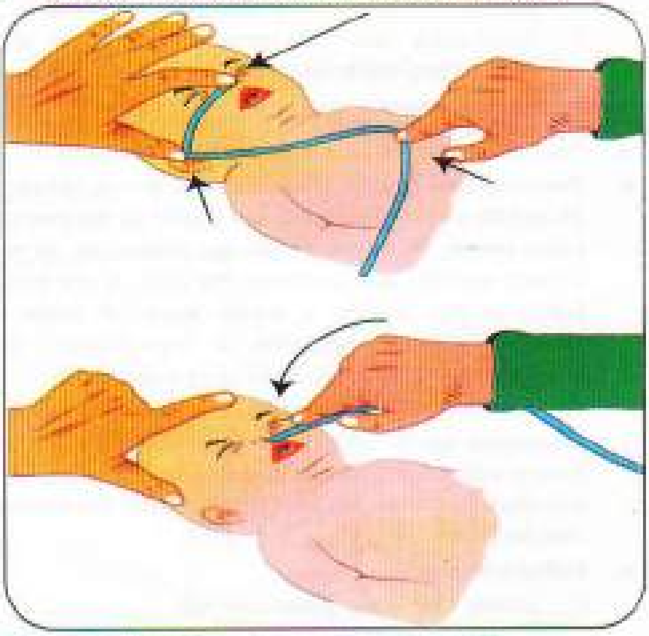


Figure 9.6: Illustration to pass nasogastric tube.

Weight 2000–2500 g (gestational age >35 weeks)

- Try breastfeeding if the infant is neurologically intact or use a bottle.
- Otherwise give NG feeding.

Weight >2500 g

- Give direct breastfeeding if the infant is neurologically intact. Otherwise give NG feeding.
- If major amount of two consecutive feeds has been aspirated, stop feeding and look for signs of sepsis, ileus, gut obstruction or necrotizing enterocolitis.

Table 9.1: Tube feeding guidelines.

(These guidelines must always be individualized based on the infant's clinical status and severity of illness. The recommended volume goal for feeding is 140–200 ml/kg/day).

Birth weight (g)	Initial rate (ml/kg/day)	Volume increase (ml/kg/day)
<800	10	10–20
800–1000	10–20	10–20
1001–1250	20	20–30
1251–1500	30	30
1501–1800	30–40	30–40
1801–2500	40	40
>2500	60	40

Iron and vitamin supplement

- Vitamin drops 0.15 ml (5 drops) once daily are recommended for preterms of less than 1800 mg body weight, full dropper for exclusively breast feed babies and half dropper for babies on preterm formulas until 1 years of age.
- Iron 2 mg/kg/day is given to all babies with birth weight less than 2.5 kg or less than 36 weeks gestation starting around 1 month and continuing until on a full solid intake.
- Folic acid 0.2 mg daily is given to babies with hemolytic anemia due to blood group incompatibilities until 12 weeks.
- Vit D 400 IU are needed in term babies on exclusive breast feeding till6 month of age. For preterm 400 to 800 IU are required till 1 year of age.

Fluid therapy

- Normal daily requirements are given below.

Table 9.2: Normal daily requirements of IV fluids.

Age	Full term (ml/kg/day)	Preterm/SGA (ml/kg/day)
Day 1	60	90
Day 2	90	120
Day 3	120	150
Day 4	140	150-180
Day 5	120-140	160-220
After 5 days	120-140	160–220

Add 30 ml for phototherapy and 20–30 ml for radiant heater.

- Ideally fluid should be adjusted (20 -40ml/kg/day),so that there should be decreased in body weight of 1-3% day in first week.

TOTAL PARENTERAL/NUTRITION (TPN)

- Total Parenteral Nutrition (TPN) is intravenous administration of all nutrients (fats, carbohydrates, proteins, vitamins, and minerals) necessary for metabolic requirements and growth.
- Parenteral Nutrition (PN) is supplemental intravenous administration of nutrients.
- Enteral Nutrition (EN) is oral or gavage feeding.
- Intravenous nutrition should be anticipated in all patients who will be allowed nothing per oral (NPO) for more than 5daysor more. TPN can be given both by peripheral vessels or through central vessels , later is preferable in long term usage.

Indications

- PN is used as a supplement to enteral feedings or as a complete substitution (TPN) when adequate nourishment cannot be achieved by the enteral route.

In newborn

- Low birth weight babies <1000 gms.
- Severe respiratory problem
- Intestinal failure due to any cause (sepsis, NEC, shortgut syndrome, atresias, etc.)
- Diaphragmatic hernia
- Tracheo-esophageal fistula
- Gastroschisis

Total energy requirements

- Energy is required for the normal metabolism of body, growth and physical activity. It varies with different age groups i.e. more calories are required for newborn babies in comparison to older children.

Table 9.3: The general principal for calculating the caloric expenditure/day.

Up to 10 Kg	100 kcal/kg
11–20 Kg	1000 kcal + 50 kcal/kg for each kg above 10 kg
Above 20 Kg	1500 kcal + 20 kcal/kg for each kg above 20 kg

- Energy should be consumed from different constituents of diets as:
  - Carbohydrates = 50%
  - Fats = 35%
  - Proteins = 15%

Fluid requirements

- Generally 100 ml of water is required for energy per 100 cal.
- But for TPN extra water is required because most of water is lost in urine due to glycosuria. So 130 ml/100 Cal should be consumed.

Caloric concentration

Dextrose	4 kcal/gm
Protein	4 kcal/gm
Fat	9 kcal/gm

Carbohydrates

- Glucose is the main source of calories for TPN.
- Concentration of glucose should not increase more than 12% in peripheral vein.
- For concentrations more than this i.e. 25%, central venous line should be used.

Lipids

- Lipids are very good source of energy and are necessary to prevent essential fatty acid deficiency.
- Commonly, soya based fatty acid preparations are available i.e. Intralipid 20%.
- Administer initially in small quantities 0.5–1 g/kg/day.
- The daily amount is increased gradually in 0.5 g/kg/day increments until daily dose equals3 -4 g/kg/day.
- 10% Intralipid provide 1.1cal/ml.

Amino acids

- Aminovel is commercially available solution, containing 5 g/dl of amino acids. OR Aminoplasmil containing 10gm/dl
- Aminovel also contains sodium 35 mEq/L, potassium 25 mEq/L, magnesium 5 mEq/L and chloride 38 mEq/L.
- Start with low dose 0.5-1 g/kg (10 ml/kg) in term babies from day 2 or 3 and in prematures of less than 1500 gm start from 2-2.5gm/kg from day 1st and then gradually increase of 1gm/kg/day in all neoborns up to 3.5-4 g/kg/day .

Electrolytes

- Electrolytes are needed for the normal metabolism of body.

Table 9.4: Daily requirements of electrolytes.

Sodium	3–4 mEq/kg/d
Potassium	1–3 mEq/kg/d
Calcium	1–3 mEq/kg/d
Magnesium	0.5 mEq/kg/d

Vitamins and trace elements

- All vitamins A, D, E, K, vitamin B complex, trace elements like Zn, Cu, molybdenium, are required for prolonged TPN.
- Available IV vitamin preparations are Multibionta and Bejectal injection. 1 cc will provide more or less Recommended Daily Allowance (RDA) of necessary vitamins except vitamin D, K, folic acid and iron, which can be provided separately if, indicated.

Monitoring of TPN

- Daily weight.
- Strict intake output record.
- Start TPN in peripheral vein and then replace with central vein if prolonged TPN is required.
- Vital signs monitoring; initially more frequently than per shift i.e. 8 hourly.
- Avoid infection by meticulous asepsis.
- Lipid infusionpreferably should be given by separate IV line or by side channel i.e. should not be mixed with other solutions.
- All vitamins, trace elements, electrolytes should be added to glucose infusion not in fat solution.
- Protein and glucose solution can be given in same bottle.
- Fats should be discontinued when phototherapy is required for hyperbilirubinemia and aminoacids withdrawn when obstructive jaundice is present.
- Stop lipid infusion 6 hours before taking blood sample for investigations.
- Keep blood glucose below 120 mg/dl. Hyperglycemia may be a sign of sepsis in very small premature infants and should be taken seriously.
- Check blood and urine glucose daily.
- Complete Blood Counts (CBC), serum electrolytes, blood urea/cretinine, liver function tests (initially daily then twice weekly).
- Ca, PO_4, Mg should be checked after every 2 weeks.
- If the patient is receiving lipids, then triglyceride level should be checked after 2 weeks.
- Coagulation profile if needed.
- Send blood culture, urine culture if fever is more than 38°C. If fever persists, then remove the catheter line.

Complications of TPN

- Infection: Candida albicans infection, Staphylococcal (*S. aureus, S. epidermidis*) sepsis. Its treatment is care of central venous line (asepsis); send culture and remove catheter if sepsis is proven.
- Cholestatic jaundice may occur; cause of this complication is amino acids competing for bile acid receptors at hepatocytes, lack of oral feeding which is necessary for cholangiopancreatic system, sepsis, and free radical damage.
- Metabolic: Hyperglycemia, hypoglycemia, acidosis, hypomagnesemia, hyperlipidemia, hyperaminoacidemia, hypocalcemia, carnitine and selenium deficiency, azotemia.
- Line related complications: Arrhythmias, venous thrombosis, air embolism,blocking of catheter.
- Complication due to intralipid: Lipid infusion displaces bilirubin for albumin (contraindicated in jaundiced infant),

BIRTH ASPHYXIA/PERINATAL ASPHYXIA

CASE

A 2-hour-old neonate delivered at home is brought for evaluation. He ***did not cry afterbirth*** for 15 minutes. On examination, child is ***pale*** with peripheral ***cyanosis***. He has irregular breathing, and heart rate is 80/minute. He is unresponsive to stimulation.

Definition

- Asphyxia is defined as lack of oxygen (hypoxia) due to failure of initiation of breathing.
- Hypoxia means arterial oxygen less than normal and ischemia means decreased blood flow to cells or organs that is insufficient to maintain their function.

Incidence

- It is usually related to gestational age and birth weight. The incidence is higher in premature.
- Incidence in developed countries is 0.1-1/1000 live births in developed countries, and quite high in developing countries

Risk factors

Maternal

- Hypertension, including eclampsia and preeclampsia
- Pelvic abnormality (cephalopelvic disproportion)
- Diabetes mellitus
- Nephritis
- Hypotension
- Infections
- Uterine tetany (due to excessive oxytocin)
- Maternal hypoxia from cardiac and pulmonary disease

Placental

- Abruptio placenta
- Placental insufficiency due to toxemia or post-maturity

Fetal

- Cord prolapse or compression
- Abnormal lie or presentation
- Postmaturity
- Anemia
- Infections
- Cerebral abnormalities
- Hypoxia due to pulmonary or cardiac problems

Pathophysiology

- The pathology depends upon the organ affected and the severity of insult.
- The onset of asphyxia is followed by:
    - Metabolic acidosis
    - Hypoglycemia
    - Hypotension
    - Alterations in cerebral blood flow
- In CNS, fluid leaks from increased capillary permeability leads to cerebral edema and cell death.
- Metabolic consequences include:
    - An acceleration of glycolysis with an increase in brain lactate levels, and A reduction in high-energy phosphate concentrations.
- At the same time, failure of energy dependent ionic pumps results in:
    - Leakage from cells of the normally intracellular potassium, and influx into cells of sodium, chloride and calcium.
    - As a consequence, membrane depolarization occurs, with concomitant release of the exitotoxic neurotransmitters, glutamate and aspartate; these in turn, activate N-methyl-D-aspartate receptors, which play a critical role in neuronal damage.
- Alterations in cerebral blood flow accompany these metabolic changes and include:
    - An initial increase in cerebral blood flow
    - Loss of vascular autoregulation
    - Reduction in cardiac output
    - Hypotension
    - Reduction in cerebral blood flow.
- The pathologic changes observed in the brain reflect the combined effects of metabolic derangements that are occurring in the context of cerebral hypoperfusion.
- Circulatory changes play a major role in the production of parasagittal cerebral injury) and periventricular leukomalacia.
- Full term infant shows cortical necrosis and parasagittal ischemic injury, which results in focal or multifocal cortical infarcts that produce focal seizures and hemiplegia.
- Preterm infants demonstrate periventricular leukomalacia (later spastic diplegia), basal ganglia damage and IVH.

Diagnosis

Before delivery

- Identification of recognized risk factors described above alerts the pediatrician to receive an asphyxiated baby in delivery room.
- Signs of fetal distress as detected by bradycardia, late decelerations, sustained tachycardia on cardiotocograph or by ultrasound showing reduced fetal activity and breathing movements or by presence of thick meconium in liquor are good pointers for birth asphyxia.

At birth

- Depression of Apgar score is the most widely used criteria for diagnosis of birth asphyxia.
- Apgar score assesses five variables easily identified at birth, which is given below.
- Sixty seconds after complete birth of the infant (disregarding the cord and placenta), the 5 objective signs listed above are evaluated, and each is given a score of 0, 1, or 2.
- A total score of 10 indicates an infant in the best possible condition. An infant with a score of 0–3 requires immediate resuscitation.
- However, a low Apgar score may not indicate asphyxia in preterm or small for gestational age infants as they are usually hypotonic at birth and have cyanotic extremities and poor responsiveness.
- Low Apgar score may be present in non-asphyxiated infants with depression from maternal anesthesia or analgesia, trauma, some neuromuscular disorders, metabolic or infectious insults to the CNS, cardiac or pulmonary malformations.
- However, it is a very good indicator that infant requires resuscitation.
- The Apgar score at 10 minutes are more strongly correlated with asphyxia and likelihood of subsequent neurological deficits and also describes the success of efforts of resuscitation.

Table 9.5: APGAR score.

	0	1	2
A Appearance (color)	Blue, pale	Body pink, extremities blue	Completely pink
P Pulse (heart rate)	Absent	Below 100	Over 100
G Grimace (response to stimulation)	No response	Facial grimace	Cough or sneeze
A Activity (muscle tone)	Limp	Some flexion of extremities	Active motion
R Respiratory effort	Absent	Slow, irregular	Good, crying

Complications of asphyxia

- CNS: Hypoxic ischemic encephalopathy,seizures infarction, intracranial hemorrhage, cerebral edema, hypotonia, hypertonia,
- Kidney: Acute tubular or cortical necrosis
- Respiratory: ARDS, persistent pulmonary hypertension, apnea, pulmonary hemorrhage
- CVS: Myocardial ischemia, tricuspid and mitral regurgitation, hypotension, cardiac failure
- GIT: Necrotizing enterocolitis, gastric ulcerations and perforation of gut
- Hematological: Disseminated intravascular coagulation
- Metabolic: Hypoglycemia, rarely hyperglycemia, hypocalcemia, hypomagnesemia and inappropriate secretion of ADH
- Hepatic : Shock liver, raised LFT's
- Skin: Subcutaneous fat necrosis
- Adrenal insufficiency (adrenal hemorrhage)

Hypoxic Ischemic Encephalopathy (HIE)

CASE

A mother presents at 40 weeks with ***reduced fetal movements***. There is fetal***bradycardia***. Emergency cesarean section is carried out. A baby boy is born and requires intubation for ***apnea***. In neonatal ICU, he remains apneic, anuric and develops ***generalized convulsions***.

- This is a condition of neonatal encephalopathy secondary to hypoxia and ischemia in the newborn infant.
- It is graded into three stages, which have prognostic significance. Infant may progress from one stage to the next stage over first 24–72 hours as the effect of hypoxia on various organs become manifest.

Diagnosis

- Diffusion-weighted MRI:
    - It is a preferred imaging modality (early in the disease process) in neonates with HIE because of its increased sensitivity and specificity.
- CT scan:
    - less sensitive and specific than MRI
- Ultrasonography:
    - Has limited ability in evaluation of hypoxic injury in the term infant.
    - It is the initial preferred modality in evaluation of the preterm infant.
- Amplitude-integrated Electro-encephalography (aEEG):
    - To diagnose subclinical fits
    - Help to determine which infants are at highest risk for long-term brain injury.

Management

- Optimal management is prevention.
- Management depends upon the early detection and management of high-risk pregnancies by regular follow up and good obstetrical care and prompt resuscitation in delivery room.
- **Whole body (systemic) or selective cerebral therapeutic hypothermia**:
    - It is the preferred treatment so far. Keep core temperature between 33-34C^{0} within first 6 hours of life for 72 hours.

Table 9.6: Stages of hypoxic ischemic encephalopathy.

Signs	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic	Stuporous, coma
Muscle tone	Normal	Hypotonic	Flaccid
Posture	Normal	Flexion	Decerebrate
Tendon reflexes/clonus	Hyperactive	Hyperactive	Absent
Myoclonus	Present	Present	Absent
Moro reflex	Strong	Weak	Absent
Pupils	Mydriasis	Miosis	Unequal, poor light reflex
Seizures	None	Common	Decerebrate
EEG	Normal	Low voltage	Burst suppression changing to isoelectric seizure activity
Duration	<24 hours	24 hours to 14 days	Days to weeks
Outcome	Good	Variable	Death, severe deficits

  - Reduces mortality or major neurodevelopmental impairment in term and near-term infants with HIE for stage II or III.

General supportive care

- Nurse the baby in thermoneutral environment if there isno facility for therapeutic hypothermia
- Record vital signs and maintain intake output record.
- Pass nasogastric tube and aspirate the stomach.
- Avoid hypoglycemia or hyperglycemia by regular glucose monitoring.
- Measure blood gases (if available).
- Keep SpO2 between 85 to 95% , give oxygen if SpO2 is less than 85%
- Treat acidosis with judicious use of soda bicarbonate (there is increased risk of hypercarbia and hypernatremia with large amount of soda bicarbonate further increasing the risk of cerebral edema).
- Maintain fluid and electrolyte balance. If there is evidence of SIADH, then restrict fluid up to 70% of normal requirement.
- Review infection risks and treat with appropriate antibiotics.
- Do not restrict maintenancefluids.

Specific management of complications

Central nervous system

- Treat seizures with phenobarbitone (20 mg/kg loading dose slow IV followed by maintenance dose of 3–5 mg/kg/day).
- Treat cerebral edema with fluid restriction and careful monitoring of electrolytes.Don't give steroids to treat the post-asphyxial cerebral edema, as it may be associated with adverse outcome.

Cardiovascular

- Treat hypotension with saline bolus and inotropic support (dopamine).
- Treat cardiac failure with digoxin and inotropic support.

Renal

- Urine output should be carefully monitored and should be more than 1 ml/kg/hour.
- If there is established renal failure then treat it conservatively as acute renal failure.

Pulmonary

- Apnea and carbon dioxide retention require IPPV.
- Meconium aspiration should be treated by proper tracheal suctioning in delivery room and respiratory support is given.
- Pulmonary hypertension is treated by inhaled nitric oxide or sildenafil.

Gastrointestinal

- Treat necrotizing enterocolitis (NEC) with proper antibiotics and by avoiding enteral feeds.

Metabolic

- Correct hypoglycemia, hypocalcemia and hypomagnesemia accordingly.

Neuro-protective strategies

- Therapeutic hypothermia (hypothermia is now emerging as standard of care for perinatal asphyxia. Underlying mechanism is decreasing cerebral metabolism, inflammation, excitotoxicity, oxidative damage, and cellular apoptosis). Total body cooling and selective head cooling are currently used strategies.
- Pharmacotherapy:
  - Magnesium Sulphate
  - Erythropoietin

Prognosis

- Overall, full-term asphyxiated infants have a mortality of 10–20% and the incidence of neurological sequelae in survivors is 20–45%.
- The prognosis depends upon the severity of asphyxia and stage of HIE. 100% of newborns with mild encephalopathy (HIE stage 1) have normal neurological outcome; 80% with moderate encephalopathy (HIE stage 2) are normal neurologically and virtually all the children with severe encephalopathy (HIE stage 3) either die (50%) or develop major neurological sequelae like cerebral palsy, mental retardation, epilepsy and microcephaly.
- Findings associated with increased risk of neurologic sequelae are:
  - Apgar score of 0–3 at 20 minutes of age.
  - Presence of multi-organ failure especially oliguria.
  - Severity and duration of hypoxic ischemic encephalopathy.
  - Presence of early onset seizures, especially if difficult to control.
  - An abnormal MRI in first 24–72 hours.
  - Severity and duration of EEG abnormalities.
  - Persistent abnormalities of brain stem function.
  - Microcephaly at 3 months of age.

PREMATURITY

CASE

A 1300 gram male baby is born via normal spontaneous vaginal delivery at ***30 weeks gestation***. Mother is 29-year-old with a history of ***incompetent cervix***. At delivery, the infant has a weak cry. There is poor respiratory effort, decreased tone and decreased response to stimulation.

Definition

- It is defined as live born infant delivered before 37 weeks from the first day of the last menstrual period.

Table 9.7: Approximate birth weight at different gestational ages.

Gestational age	Mean birth weight
24 weeks	600 g
25 weeks	750 g
26 weeks	850 g
28 weeks	1000 g
30 weeks	1400 g
32 weeks	1750 g
34 weeks	2000 g
36 weeks	2500 g
38 weeks	3000 g
40 weeks	3500 g

Incidence

- The exact incidence of prematurity in Pakistan is not known but it is estimated to be 11–13%. It includes both small for gestational age (SGA) and appropriate for gestational age (AGA) infants.

Etiology

Maternal causes

- Malnutrition and anemia
- Teenage pregnancy or multi-parity
- Twin pregnancy
- Pre-eclampsia
- Chronic illness like diabetes, renal disease, heart disease, hypertension, etc.
- Infection like malaria, UTI, chorioamnionitis
- Lower socioeconomic status
- Smoking or drug abuse
- Illegitimate birth

Uterine causes

- Bicornuate uterus
- Incompetent cervix (premature dilatation)
- Placenta previa, Abruptio placentae, placental dysfunction

Fetal causes

- Fetal distress
- Multiple gestation
- Chromosomal disorders like Down syndrome
- Intrauterine infections like syphilis, toxoplasmosis, etc.
- Erythroblastosis, Non-immune hydrops

Others

- Polyhydramnios
- Trauma
- Premature rupture of membranes
- Iatrogenic

Problems of prematurity

Immediate (acute)

Hypothermia

- It occurs in preterm babies due to:
  - High surface area to body weight ratio
  - Little subcutaneous fat
  - Muscular inactivity
  - Inadequate sweating mechanism
  - Decreased brown fat
  - Immature heat regulation mechanism

Hypoglycemia

- It is common due to lack of glycogen stores and immature hepatic and autonomic responses.

Hypocalcemia

- Early hypocalcemia occurs due to immaturity of hormonal control system.

Respiratory difficulties

- Hyaline membrane disease due to surfactant deficiency leading to IRDS.
- Apneic spells: The immaturity of respiratory centre may lead to periodic breathing and frequent apneic spells.

Intraventricular Hemorrhage (IVH)

- It is common in preterm infants due to:
  - Immature vasculature.
  - Disturbed cerebral auto-regulation of blood flow.
  - Clotting factor deficiency.

Liver immaturity

- It results in prolonged physiological jaundice due to immaturity of liver enzymes and there is increased risk of kernicterus at relatively lower bilirubin level.

Increased susceptibility to infections

- It results from lack of the protective maternal immunoglobulins (IgG), which is transferred across the placenta during the last trimester.
- In addition to this, delicate surfaces of skin and mucous membrane also predispose to infections.
- Insertion of IV cannulas, endotracheal tubes, nasogastric tubes also increase the risk of infection.

Nectrotizing Enterocolitis (NEC)

- There is increased susceptibility to NEC due to immaturity of gut endothelial surfaces and enzymes deficiencies.
- The risk increases with lack of breastfeeding, rapid administration of enteral feeding and septicemia.

Patent ductus arteriosus

- The duct may remain open in premature babies leading to heart failure.

Feeding problems

- These result from uncoordinated sucking and swallowing and also from gastroesophageal reflux leading to frequent aspirations.

Anemia of prematurity

- Anemia occurs due to decreased iron stores, short RBCs half-lives, multiple labs,vitamin E deficiency, and exaggerated physiological anemia.

Retinopathy of prematurity

- There is abnormal vascularization due to immaturity and oxygen therapy leading to partial or complete blindness.

Metabolic bone disease of prematurity

- There is lack of substrate (calcium and phosphate) and Vitamin D deficiency resulting in rickets.

Long term problems

Chronic lung disease (bronchopulmonary dysplasia)

- Prolonged ventilation and oxygen toxicity results in chronic oxygen dependency.

Poor growth

- Growth is retarded due to feeding problems, vitamin and iron deficiency.

CNS dysfunctions

- Cerebral palsy due to intraventricular hemorrhage
- Post hemorrhagic hydrocephalus
- Learning problems
- Deafness
- Mental subnormality

Assessment of gestational age

- Gestational age can be assessed appropriately in weeks by simple visual assessment of certain physical signs and more accurately by using Ballard scoring system.

The expanded New Ballard Score

- Physical and neuromuscular criteria of maturity are given in Expanded New Ballard Score (NBS). It now also includes extremely premature infants and has been refined to improve accuracy in more mature infants.
- In Ballard score, physical and neurologic scores are added and by this added score, gestational age is calculated.
- This score is accurate within 2 weeks of gestation in infants weighing >999 g at birth and is most accurate at 30–42 hours of age.

Table 9.8: Rapid visual assessment of gestational age

Physical signs	Assessment	Gestational age
Sole creases	*Absent*	*32 weeks or less*
	1–2 anterior sole	36 weeks
	All over sole	40 weeks
Breast nodule	Not palpable	34 weeks
	3 mm	36 weeks
	4–10 mm	40 weeks
Scalp hair	Short fuzzy	37 weeks
	Coarse, individual	40 weeks
Ear cartilage	Poorly developed	32–34 weeks
	Well developed	36–40 weeks
Testicular descent	Undescended	28 weeks
	Inguinal region	32 weeks
	Complete descent	40 weeks in 90%
Scrotal rugae	Anterior	36 weeks
	Entire scrotum	40 weeks

Management

- The management of preterm baby is based upon the proper anticipation and prevention of complications.

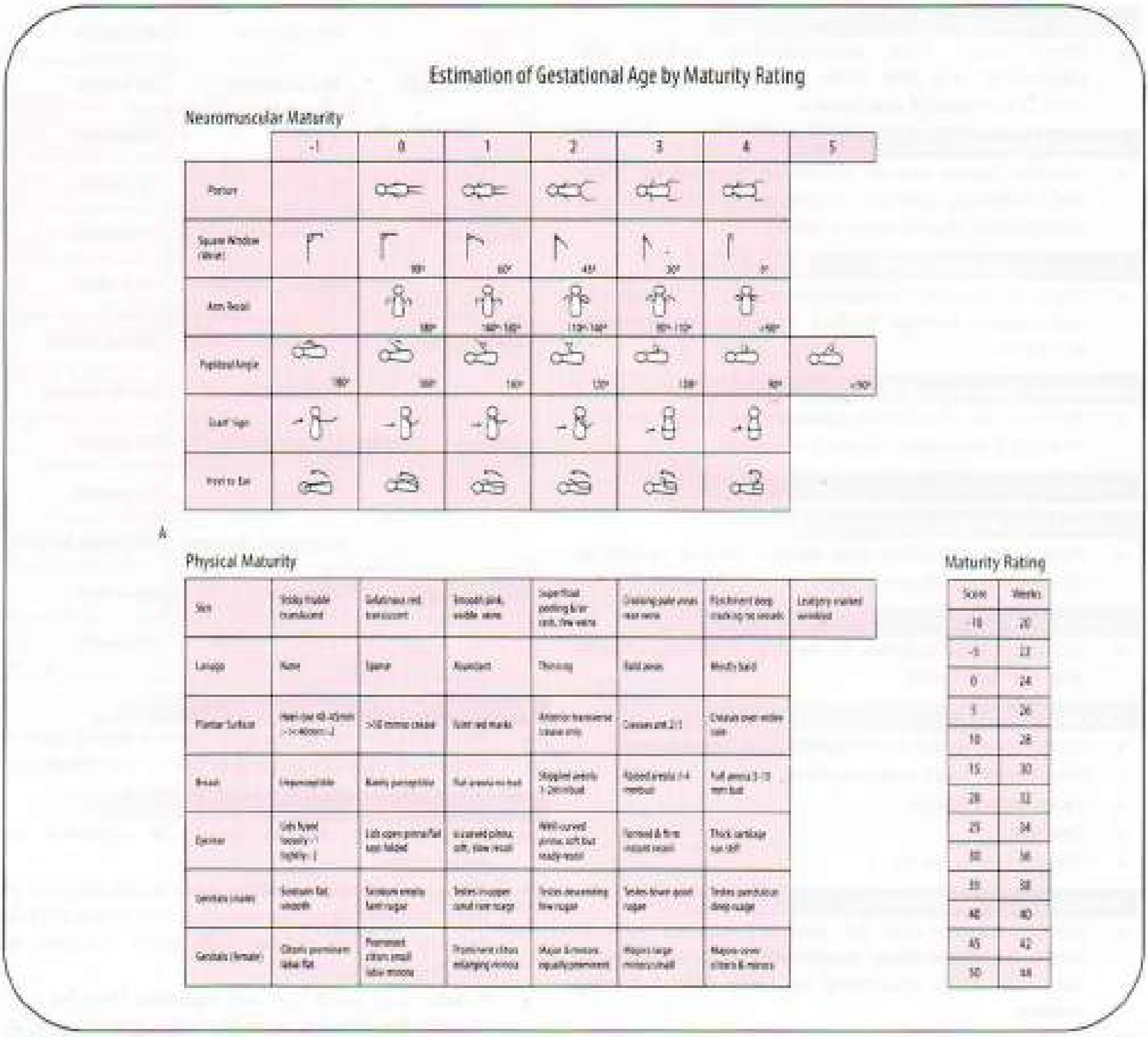
Delivery room care

- Every preterm delivery should be attended by a pediatrician.
- Proper resuscitation at birth, early stabilization of vital signs, prevention of hypothermia, and hypoglycemia in delivery room is related with good outcome with minimal complications.
- If baby is of good size and vigorous, then by simply clearing the airways, wrap the baby properly and shift to well-baby nursery with instruction of early feeding and monitoring for hypoglycemia and hypothermia.
- If baby weight is very low <1 kg, then electively intubate the baby and shift to NICU for ventilator care.
- Babies weighing 1–1.5 kg should also be shifted to NICU for observation and management of potential problems.
- Provide delivery room CPAP, if there is respiratory distress right after birth.
- For temperature control while resuscitation , apply baby hat, use polythene plastic bags and heating mattress

After birth care

Maintain thermoneutral environment

- *It is environmental temperature at which heat* production and O_2 consumption is minimal yet the core temperature is maintained within normal range.


Estimation of Gestational Age by Maturity Rating
Neuromuscular Maturity
-1
0
1
2
3
4
5
Posture
Square Window (Wrist)
Arm Recoil
Popliteal Angle
Scarf Sign
Heel to Ear
A
Physical Maturity
Skin
Lanugo
Plantar Surface
Breast
Eye/Ear
Genitals (male)
Genitals (female)
Maturity Rating
Score
Weeks
-10 20
-5 22
0 24
5 26
10 28
15 30
20 32
25 34
30 36
35 38
40 40
45 42
50 44

9.10: Now Ballard score for assessment fetal maturation of newly born infants.

- Maintain temperature of nursery in range of 25–30°C.
- Place the baby in incubator. Keep humidity at 70%.
- Temperature of incubator varies with age by setting air temperature or by setting skin temperature of baby.

>2 kg	31–33°C
1.5–2.0 kg	32–34°C
1.0–1.5 kg	32–35°C
<1 kg	35–37°C

- Temperature can be maintained by the use of radiant heaters, by wrapping the baby properly and by the use of mitten on hand and socks on feet and cap on head if nursed in cot.

Maintenance of fluid and electrolyte balance

- Premature babies need more fluids as compared to full term infants.
- Baby should be carefully monitored for hypoglycemia, hypoor hypernatremia, and hyperkalemia, etc. by frequent blood sample checking and their correction.
- Daily increase in fluid requirement also depends upon on use of humidity in incubators , baby daily weight change. Ideally, weight change should not be more than 1-3% day.

Table 9.9: Fluid requirement of premature baby.

1st day	60–80 ml/kg/day
2nd day	80–100 ml/kg/day
3rd day	100–110 ml/kg/day
4th day	120–130 ml/kg/day
5th day and onwards	150–180 ml/kg/day

Oxygen administration

- O_2 administration should be carefully monitored in a very premature infant because excessive use of O_2 increases the risk of lung and visual toxicity (Bronchopulmonary dysplasia and retinopathy of prematurity).

Feeding

- The method of feeding should be individualized as it varies with weight and gestational age of infant.
- The process of oral feeding in addition to sucking requires coordination of swallowing, epiglottic closure of the larynx, normal esophageal motility, a synchronized process, which is usually absent prior to 34 weeks gestation.
- If the infant is more than 35 weeks gestation, weighing >2 kg and there is no contraindication of feeding like persistent vomiting, RDS, sepsis, seizures, etc., he should be started on oral feeding preferably by breast milk or infant formula with bottle or cup and spoon.
- If baby cannot suck and general condition is better, tube feeding is preferred.
- If very sick or premature, then total or partial parenteral nutrition is the choice.

Supplementation of iron and vitamins

- Every preterm infant should receive supplement vitamins in addition to breast milk until 6-12 months afterbirth.
- All preterm babies should receive vitamin K prophylaxis 1 mg vitamin K at birth.
- Vitamin E in dose of 25 IU/day should be given to babies less than 1.5 kg or having prolonged illness.
- Requirement of vitamin A, D, B6, and C is fulfilled by simply prescribing 0.6 ml Vidaylin drops per oral.
- Iron supplementation should be started at the age of 6–8 weeks at dose of 2 mg/kg/day. Before this age it is not well absorbed and also increases the risk of gestrointestinal infection and also predisposes to vitamin E deficient hemolysis
- Those prematures who areon premature formula milk should be given half dosage of multivitamins drops.

Protection from infection

- Proper antiseptic measures should be taken in maintenance of nursery, incubator and other equipment, and in addition proper hand washing, cleansing of preterm baby, proper cord care are very important.
- All procedures in nursery should be done with strict aseptic measures.

Early detection and management of complications of prematurity

- It can be done by good nursery care, monitoring of heart rate, respiratory rate, temperature, blood pressure, activity, daily weight, and intake and output record.
- Oxygen saturation monitoring is very important in care of preterm babies.

Immaturity of drug metabolism

Due to renal and hepatic immaturity and diminished renal and hepatic clearance of almost all drugs, intervals between doses should be extended.

Prognosis

- It is related to gestation and birth weight.
- With new advancement in neonatal intensive care in developed countries, the survival rate for 24 weeks gestation is 25%. But still there is marked disability in survivors.
- 5–10% of babies with birth weight less than 1500 gm have major handicap such as cerebral palsy, developmental delay, blindness or deafness.
- Risk increases with decreasing gestational age and weight.

Discharge criteria for preterm

- A premature infant should be taking feeding by nipple (either bottle or breastfeeding).
- Baby should be gaining weight properly (10–30 g/day).
- Temperature should be stabilized in an open cot.
- There should be no recent episode of apnea or bradycardia.
- There should be no parenteral drug administration; it may be converted to oral dosing.

CAUSES OF RESPIRATORY DISTRESS IN THE NEWBORN INFANT

CASE

A newborn infant is born at 31 weeks' gestation (***preterm***) following a placental abruption. He requires bag/mask ventilation. He presents with ***tachypnea, grunting*** respirations, and deep ***intercostal retractions***. Arterial blood gas shows high PCO_2 and low PO_2 (***respiratory acidosis***). A chest radiograph shows uniform reticulogranular pattern (***ground glass appearance***) of the lung fields with peripheral ***air bronchogram***.

Definition

- It is defined as respiratory rate >60/minute with significant chest indrawing.

Causes

Lung disorder due to aspiration

- Intrauterine pneumonia
- Meconium aspiration
- Milk aspiration

Delay in clearance of lung liquid

- Transient tachypnea of newborn

Disorder due to lung immaturity

- Idiopathic respiratory distress syndrome (hyaline membrane disease)
- Bronchopulmonary dysplasia
- Pulmonary hemorrhage
- Apneic attacks
- Air leaks like pneumothorax

Congenital malformations

- Diaphragmatic hernia
- Bilateral choanal atresia
- Tracheo-esophageal fistula

Extra-pulmonary causes

- Cerebral anoxia (birth asphyxia)
- Intracranial hemorrhage
- Metabolic acidosis
- Persistent pulmonary hypertension
- Cardiac failure, congenital heart disease

RESPIRATORY DISTRESS SYNDROME (RDS) or HYALINE MEMBRANE DISEASE

- Respiratory distress syndrome occurs primarily in premature infants.

Definition

- RDS is a clinical diagnosis in a preterm newborn with:
  - Respiratory difficulty including tachypnea (>60 breaths/minute)
  - Chest retractions
  - Cyanosis that persists or progresses over the first 48–96 hours of life
  - A characteristic chest X-ray film (uniform reticulo-granular pattern and air bronchogram)

Pathophysiology

- Surfactant deficiency (decreased production and secretion) is the primary cause of RDS.
- Surfactant is a surface-active material produced by type–II alveolar cells. Surfactant synthesis begins at 24–28 weeks' gestation.
- Surfactant deficiency results in progressive atelectasis, ventilation-perfusion mismatch and inadequate gas exchange. Hypoxia, acidosis, and CO_2 retention further impairs surfactant release resulting in respiratory failure.

Incidence

- The incidence of RDS is inversely proportional to gestational age.
- RDS severe enough to require assisted ventilation occurs in 25% of infants born at 30 weeks gestation.
- RDS accounts for 20% of all neonatal deaths.
- There are certain known risk factors, which increase incidence of RDS.

Risk factors

- Prematurity
- Male sex
- Chorioamnionitis
- Hydrops fetalis
- Infant of diabetic mother
- Cold stress
- Perinatal asphyxia
- Maternal diabetes
- Cesarian section without labor

Clinical findings

- The natural history of classical RDS is that of increasing severity during the first 24–48 hours of life, followed by a period of stability lasting for another 48 hours before improvement occurs.
- The disease has varying clinical features depending upon severity of the disease.
- Early clinical signs of RDS are:
  - Tachypnea >60/minute
  - Expiratory grunting, nasal flaring
  - Sternal and intercostal recessions
  - Cyanosis in room air
  - Delayed onset of respiration in very premature baby
- In severe disease or in very premature babies, symptoms and signs appear in labor room and they need positive pressure ventilation.
- In mild to moderate disease symptoms appear gradually but within first 6 hours, and infant becomes hypoxic, requiring increased oxygen and respiratory support becomes necessary.

Differential diagnosis

- Transient tachypnea of newborn
- Congenital pneumonia (early onset sepsis)
- Aspiration pneumonia
- Meconium aspiration
- Pneumothorax
- Diaphragmatic hernia
- Cyanotic heart disease

Investigations

- **Chest X-ray:**
  In early RDS, there is fine reticulogranular mottling progressing to appearance of air bronchograms and finally bilateral white out.
- **Septic screen:** Complete blood counts and blood, urine and CSF culture to rule out early onset sepsis.
- **Arterial Blood Gases (ABGs)** to look for evidence of hypoxia and acidosis.
- **Pulse oximetry** to monitor oxygen saturation.
- **Hyperoxia test** to differentiate between cardiac and pulmonary etiology in infants who have cyanosis.
- **Blood sugar and calcium levels.**

Management

- The basic defect requiring treatment in RDS are:

  - Inadequate pulmonary exchange of oxygen and carbon dioxide ,leading to hypoxia and metabolic acidosis and which eventually depress the myocardium and result into circulatory insufficiency

General, supportive care

- Maintain neutral thermal environment.
- Keep careful monitoring of fluid and electrolytes especially prevent hypoglycemia.
- Minimal handling of baby is very important.
- Withhold feeding till baby stabilizes.
- Keep intake and output record as diuresis is a sign of improvement.
- Carefully monitor oxygen saturation (SaO_2) by pulse oximetry to detect hypoxia earlier.
- Keep blood pressure of baby in normal limits by use of saline or inotropes.
- Treat metabolic acidosis by giving soda bicarbonate

Specific management

- Warm humidified **oxygen** should be given to maintain PaO_2 between 50–70 mmHg (90–95% saturation).
- Hyperoxia may contribute to lung injury in preterm infants. Therefore, the currently recommended range of oxygen saturation targets is 91–95%.
- **CPAP:** Continuous Positive Airway Pressure is a respiratory support by which a continuous distending pressure is applied by nasal prongs through bubble CPAP,flow driver or ventilators to prevent alveolar collapse. Early use of CPAP for stabilization of at-risk preterm infants beginning as early as in the delivery room reduces ventilatory needs.
- **Humidified High Flow Nasal Cannula :is an emerging respiratory support having more ease to baby and less side effect like pneumothorax than CPAP.**
- **IPPV:** Intermittent positive pressure ventilation is required when there is respiratory failure, frequent apneic attacks, or failure of baby to establish respiration at birth.
- **Surfactant replacement therapy:**It has dramatic effects in the treatment of RDS and by its use there is marked decrease in mortality in preterm babies.Babies with RDS should be given an animal-derived surfactantpreparation . A policy of early rescue surfactant should be standard , buthere are occasions when surfactant should be given in the deliverysuite, such as when intubation is needed for stabilization. Babies with RDS should be given rescue surfactant early inthe course of the disease. A suggested protocol would be totreat babies who are worsening when FIO2 > 0.30 on CPAPpressure of at least 6 cm H2O . Poractant alfa (Curosurf, pork derived preparation) at an initial dose of 200 mg/kg is better than 100 mg/kg of poractant alfa or 100 mg/kg of beractan (Survanta,,bovine derived preparation)t for rescue therapy. A second and occasionally a third dose of surfactant should begiven if there is ongoing evidence of RDS such as persistent highoxygen requirement and other problems have been excluded. Surfactant should be given in those units where full neonatal intensive care facilities with ventilator are available.
- Surfactant can also be given in meconium aspiration, persistent, persistent pulmonary hypertension and congenital pneumonia.
- The potential complications of surfactant therapy are endotracheal blockage, pneumothorax and pulmonary hemorrhage.
- Periodic monitoring of PaO_2, $PaCO_2$, and pH is an important part of the management (such monitoring is essential for assisted ventilation).
- Oxygenation (oxygen saturation) may be assessed continuously from transcutaneous electrodes or pulse oximetry.
- Because of the difficulty of distinguishing sepsis (group B streptococcal or other bacterial infections) from RDS, antibiotic therapy is indicated before the results of blood cultures are available. Penicillin or ampicillin with an aminoglycoside is recommended.

Complications of RDS

- Patent ductus arteriosus
- Intraventricular hemorrhage
- Pulmonary complications like air leaks (pneumothorax)
- Bronchopulmonary dysplasia
- Pneumonia
- Complications of mechanical ventilation

Prevention

- Prevention of prematurity by:
  - Avoidance of unnecessary or poorly timed caesarean sections
  - Appropriate management of high-risk pregnancy and labor
  - Prediction and possible in utero acceleration of pulmonary immaturity
- Administration of betamethasone (dexamethasone) to woman 48 hours before delivery of fetus between 24–34 weeks of gestation decreases the severity of RDS.

Prognosis/outcome

- It depends upon the gestation and level of nursing care.
- Surfactant therapy has reduced mortality from RDS approximately 40%.
- Chronic lung disease incidence has not been affected.

BRONCHOPULMONARY DYSPLASIA

CASE

A ***preterm infant*** at birth required oxygen due to ***respiratory distress syndrome***. Now infant is 7 week old. He has been extubated for 2 weeks and ***still***

requires oxygen to maintain her saturation above 93%. Chest X-ray shows patchy, fluffy infiltrates with areas of lucency. Now he is on ***daily diuretic treatment***.

- Bronchopulmonary Dysplasia (BPD) is a pathologic process leading to signs and symptoms of chronic lung disease.
- It develops in preterm neonates treated with oxygen and positive-pressure ventilation.
- Definition includes oxygen requirement for 28 days postnatally.

Clinical findings

- Tachypnea, tachycardia, increased respiratory effort (with retractions, nasal flaring, and grunting) and frequent desaturations are common finding.
- There is increased anteroposterior diameter due to air trapping.
- Intercostal retractions are present.
- There is baseline wheeze or coarse crackles.
- Supplemental oxygen may be required to maintain oxygen saturation and is needed to minimize the work of breathing.
- Infants with significant lung disease have growth failure from the elevated energy expenditure essential to maintain the increased metabolic demands of respiration.
- Chronic respiratory insufficiency may occur.
- A pulmonary exacerbation of BPD may occur during viral respiratory infections.

Diagnosis

- Arterial blood gas (ABG) levels: To assess for acidosis, hypercarbia, and hypoxia (with increased oxygen requirements).
- Pulmonary function tests.
- Chest radiography to demonstrate decreased lung volumes, areas of atelectasis and hyperinflation, pulmonary edema, and pulmonary interstitial emphysema.

Management

- Goals of treatment are to:
  - Decrease the work of breathing
  - Normalize gas exchange
  - Maintain optimal growth and neurodevelopment.
- Main management strategies are:
- Surfactant replacement with optimal oxygen supplementation reduces the risk of BPD.
- Continuous positive airway pressure (CPAP)
- Mechanical ventilation but of less aggressive approach also reduces the risk of BPD.
  - Inhaled bronchodilator is frequently used for wheezing. It increase air movement and improve comfort of breathing, resulting in short-term improvement in pulmonary function values.
  - The administration of preventive anti-inflammatory medications, such as inhaled glucocorticoids agents are used to treat and prevent inflammatory triggers.
  - Supplemental oxygen therapy is indicated to improve oxygen saturation values and reduce the risk of cor pulmonale.
  - Diuretic therapy (furosemide or thiazides) may improve pulmonary mechanics by decreasing lung water.
  - Adequate caloric intake is important.
  - Prognosis for infants with BPD is generally good.

NECROTIZING ENTEROCOLITIS (NEC)

CASE

An infant, born at 32 weeks' gestation (***preterm***) is now 10 days old. He was doing well on increasing enteral feedings. Now, he has bilious vomiting for last 2 hours (***feeding intolerance***). He has a ***grossly bloody stool***. On clinical examination, he is lethargic and bradycardiac. He has a tense and ***distended abdomen*** with decreased bowel sounds and bilious aspirates. ***Pneumatosis intestinalis*** (intramural gas) and bowel wall thickening is found on plain radiograph of the abdomen.

Definition

- Necrotizing Enterocolitis (NEC) is an acquired neonatal disorder representing an end expression of serious intestinal injury following a combination of vascular, mucosal, and toxic insults to a relatively immature gut.

Incidence

- Affected infants most commonly are premature.
- Infants with NEC represent 1.7–7.0% of neonatal intensive care unit admissions.

Pathophysiology

- Bowel ischemia secondary to preceding perinatal asphyxia generally is regarded as the cause of bowel wall injury.
- The introduction of milk then provides the substrate for bacterial overgrowth.
- Bacterial invasion of the bowel wall, often with gas production (pneumatosis intestinalis), leads to tissue necrosis and perforation.

Predisposing factors

- Prematurity (immaturity of circularity, gastrointestinal, and immune systems).
- Asphyxia and acute cardio-pulmonary disease.
- Enteral feeding provides necessary substrate for proliferation of enteric pathogens.
- Hyperosmolar formula may cause direct mucosal damage.
- Polycythemia and hyperviscosity syndromes.

- Exchange transfusions
- Rapid advancement of the feeding volume.
- Use of drugs (indomethacin,).

Clinical findings

- Age of onset varies inversely with gestational age. In preterm infants disease may develop at several weeks of age. In term infants, 2 days is median age of onset.

Gastrointestinal

- Gastric residuum (delayed gastric emptying), which often is bile stained (feeding intolerance).
- Vomiting
- Abdominal distention.
- Abdominal tenderness.
- Blood in stool (occult or gross).
- Poor perfusion, with hypotension or shock.
- Abdominal wall discoloration (erythema).

Systemic

- Lethargy
- Apnea
- Poor perfusion, with hypotension or shock
- Unstable temperature
- Hyperglycemia
- Metabolic acidosis
- Disseminated Intravascular Coagulation (DIC).

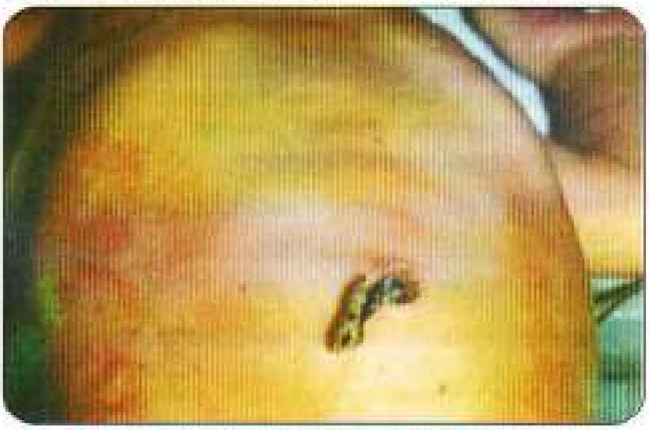


Figure 9.7: A newborn with abdominal distension due to necrotizing enterocolitis.

Diagnosis

- Triad of:
  1. Feeding intolerance
  2. Abdominal distension
  3. Grossly bloody stools
- CBC (leukocytosis or neutropenia thrombocytopenia)
- Supportive findings on abdominal radiography:
  - Dilated, thickened bowel loops. Fixed sentinel loop of bowel
- Confirmatory findings on abdominal radiography are:
  - Pneumatosis intestinalis (air in the bowel wall)
  - Perforation, with free abdominal gas and portal vein gas
  - Portal vein gas (in severe disease)
  - Pneumoperitoneum (in perforation of intestine)
- Hepatic Ultrasonography (USG) shows gas in portal vein in some cases
- Blood culture for aerobes and anaerobes
- Stool screening for occult blood
- Arterial blood gases, serum electrolytes, coagulation profile

Differential diagnosis

- Neonatal sepsis
- Intestinal malrotation
- Intestinal volvulus
- Hirschsprung disease

Management

- Rapid initiation of treatment is very important step
- There is no treatment of necrotizing enterocolitis once established
- A supportive treatment is needed to prevent further injury to intestine
- Discontinuation of enteric feeding (in severe cases NPO for1- 2 weeks and give TPN)
- Gastric drainage by using nasogastric tube
- Administration of intravenous fluids or blood
- Strict intake and output monitoring
- Correction of hematologic, metabolic, and electrolyte abnormalities
- Close monitoring of vital signs and abdominal circumference
- Remove umbilical catheter (if present)
- Send blood for culture and coagulation profile
- Systemic antibiotics , usually broad spectrum.
- Any accompanying disorder (e.g. DIC) should be treated
- Surgical resection of the necrotic bowel segment is indicated for infants who have had a progressive deterioration and for those in whom intestinal perforation has occurred.

Prognosis

- The mortality rate associated with necrotizing enterocolitis is highest in the most premature infants. It is approximately 30%.

Prevention

- Breastfeeding reduces the risk of NEC.
- Avoid hyperosmolar feeds.
- Avoid very rapid advancement of enteral feed.
- Use of probiotics with or without prebiotics

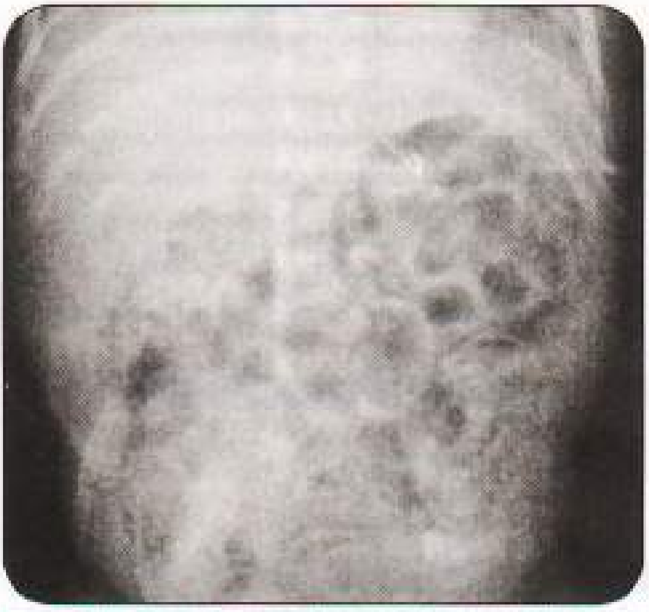


Figure 9.8 : X-ray showing Pneumatosis intestinalis due to necrotizing enterocolitis.

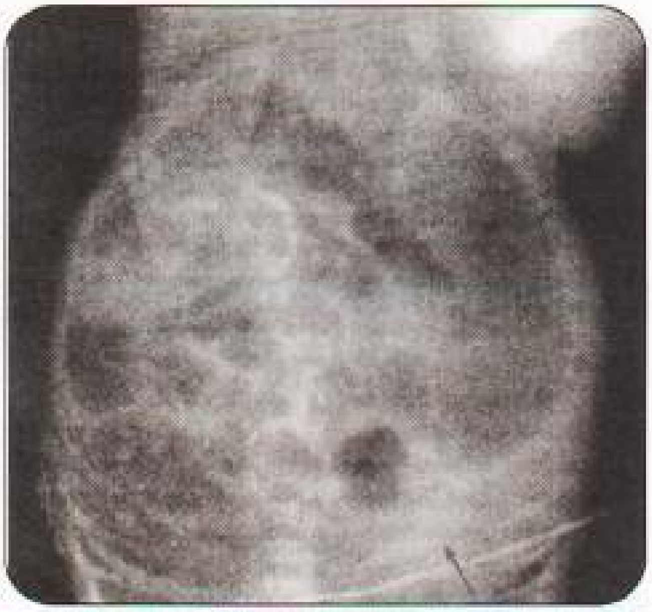


Figure 9.9 : X-ray abdomen showing abdominal dictension due to necrotizing enterocolitis.WRONG POSITION

INTRAVENTRICULAR HEMORRHAGE (IVH)

CASE

A ***premature*** (seven month gestational age) infant presented with ***pallor***, lethargy and ***seizures***. On examination, his ***fontanel*** was ***bulging***. IVH was confirmed on cranial USG.

Definition

- Intraventricular hemorrhage is an intracranial hemorrhage that originate in the periventricular subependymal germinal matrix with subsequent entrance of blood into the ventricular system.
- It is mainly a disorder of preterm infants.
- **Early IVH** is defined as IVH within 72 hours after birth.
- **Late IVH** is defined as IVH after 72 hours of life.

Incidence

- Incidence and severity of IVH are inversely proportional to gestational age.
- Overall incidence is 20% in infants weighing <1500 g at birth.
- The risk period of IVH is during the first 3–4 postnatal days.

Pathogenesis

- The germinal matrix is a weakly supported and highly vascularized area.
- It is located between the caudate nucleus and thalamus. The blood vessels in these areas represent the "watershed zone", and are prone to hypoxic-ischemic injury. These vessels are irregular and are prone to rupture in babies <1500 g weight and <34 weeks gestation.
- Fluctuations in cerebral blood flow play an extremely important role in sick premature infants. A sudden rise in systemic blood pressure may result in an increase in cerebral circulation with subsequent rupture of the germinal matrix vessels. Decreases in cerebral blood flow can result in ischemic injury to germinal matrix vessels, which rupture on re-perfusion.

Classification

- The severity of hemorrhage may be defined on cranial ultrasonography by the location and degree of bleeding and ventricular dilation.

Table 9.10: Grading the severity of intraventricular hemorrhage with ultrasound scans.

Grade I:	Germinal matrix hemorrhage
Grade II:	IVH without ventricular dilatation
Grade III:	IVH with ventricular dilatation
Grade IV:	IVH with parenchymal involvement

Risk factors

- Extreme prematurity
- Prolonged and difficult labor
- Birth asphyxia
- Vigorous resuscitation at birth
- Ventilated preterm infants
- Pneumothorax
- Seizures
- Sudden elevation in arterial blood pressure (rapid volume expansion) and administration of hypertonic fluids (sodium bicarbonate, etc).
- Hypothermia, acidosis, disturbances of hemostasis

Clinical findings

- IVH may be totally asymptomatic (especially in some cases of grade I and II intraventricular hemorrhage), or there may be subtle symptoms e.g.
    - A sudden drop in hematocrit
    - Apnea
    - Bradycardia
    - Acidosis
    - Cutaneous mottling
    - Seizures
    - Change in muscle tone or level of consciousness (absent Moro reflex, failure to suck well, a high pitched cry)
- In large IVH, there may be:
    - Rapid onset of coma
    - Seizures
    - A bulging fontanel
    - Decerebrate posturing
    - Pupils fixed to light
    - Respiratory irregularities
- Up to 50% of hemorrhages occur before 24 hours of age, and about all of them occur by the fourth day.

Differential diagnosis

- Cerebral edema due to birth asphyxia
- Sepsis, meningitis
- Hypoglycemia, hypocalcemia

Diagnosis

- Intracranial hemorrhage is suspected in a premature infant on the basis of the history, clinical manifestations, and knowledge of the birth-weight-specific risks for intraventricular hemorrhage.
- Ultrasonography (USG) is procedure of choice for diagnosis and classification of IVH. It is indicated in all infants <1000 g weight within first 72 hours, in above gestations or weight within first week and in other infants if any risk factor of IVH is present; or in the presence of raised intracranial pressure or hydrocephalus.
- Complete blood count (CBC), hemoglobin, septic screen or bleeding profile if indicated.

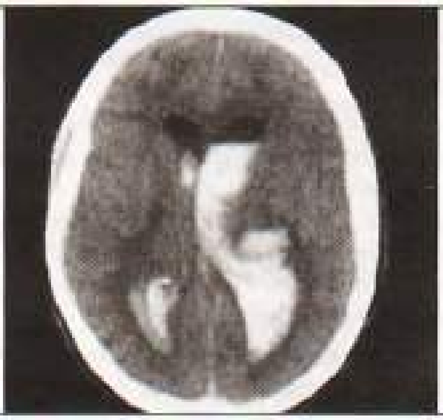


Figure 9.10: CT Scan brain showing IVH.

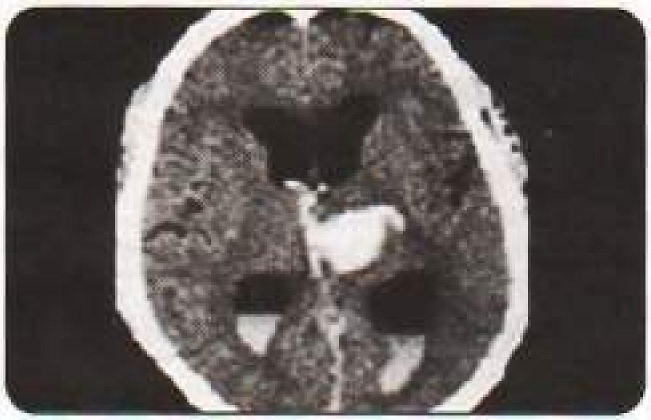


Figure 9.11: CT Scan brain showing IVH.

Prevention

Prenatal/antenatal prevention

- Avoidance of preterm delivery
- Judicious management of cephalopelvic disproportion and operative delivery may prevent traumatic IVH in older infants.
- Vitamin K should be given before delivery to all women receiving phenobarbitone or phenytoin during pregnancy
- Cesarean section in high-risk deliveries.
- Antenatal use of steroids lowers the risk of IVH especially in prematures.

Postnatal prevention

- Avoid birth asphyxia
- Avoid large fluctuations in blood pressure
- Avoid rapid infusion of volume expanders or hypertonic solutions
- Avoid excessive handling of high-risk neonates
- Avoid aggressive ventilation with high PEEP or CPAP.
- Correct acid-base and coagulation abnormalities.

Management of IVH

- General supportive care to maintain a normal blood volume and a stable acid-base status. Ventilation for apnea, blood transfusion for shock, anticonvulsant drugs for seizures.
- Avoid fluctuations of arterial and venous blood pressures.
- Serial USG or CT scanning to detect and then manage hydrocephalus.
    - An initial follow-up scan should be done 1–2 weeks after the initial scan.
    - Infants with intraventricular hemorrhage and ventricular enlargement should be followed every 7–10 days until ventricular enlargement stabilizes or decreases.

Complications

- Hydrocephalus
- Epilepsy
- Microcephaly

- Irreversible brain damage
- Shock and death

Prognosis

- There are no deaths as a result of grade I and II hemorrhage, whereas grade III and IV hemorrhage carry a mortality rate of 10–20%.
- Post-hemorrhagic hydrocephalus is rarely seen in grade I hemorrhage, but is seen in 54–87% of grade II–IV hemorrhage.

APNEA

CASE

A preterm 1.2 kg weight newborn of 6 hours age presents with ***apneic spells*** for last 2 hours. She was delivered at home and is not taking feed. On examination, ***fontanel*** is ***bulging***.

Definition

- Apnea is the cessation of breathing for >15 seconds in a term infant or 20 seconds in a preterm infant or for any duration if it is associated with decrease in heart rate, i.e. bradycardia (a heart rate <100 beats/minute) and or cyanosis.

Incidence

- Apneic spells occur frequently in premature infants. The incidence of apnea increases with decreasing gestational age. 55–65% of preterm infants present with apnea.
- Apneic spells occurring in infants at or near term are always abnormal and are nearly always associated with serious identifiable causes such as birth asphyxia, seizures, IVH, etc.

Types of apnea

Central apnea

- When there is no central neurologic drive to breathe, there is no chest wall or abdominal movements.

Obstructive apnea

- When airway obstruction results in apnea, chest wall and abdominal movements will be present in the absence of airflow at the nose and mouth.

Mixed apnea

- A combination of central and obstructive apnea can occur. It usually begins with central apnea followed by airway obstruction. Most common form for prolonged apnea.

Apnea of prematurity

- Idiopathic apnea appears in the absence of any other identifiable disease states during the 1st week of life and resolves by 36 weeks of post-conceptional age (gestational age + postnatal age).
- It is more common <34 weeks or birth weight <1800 g.

Causes of apnea

Central nervous system

- Birth asphyxia
- Intraventricular hemorrhage
- Neonatal seizures

Respiratory system

- Pneumonia
- Obstructive airway lesions
- Atelectasis
- Extreme prematurity
- Phrenic nerve paralysis

Infections

- Sepsis
- Meningitis

Gastrointestinal system

- Necrotizing enterocolitis
- Gastroesophageal reflux

Metabolic causes

- Hypoglycemia
- Hypocalcemia
- Hypo or hypernatremia
- Hypo or hyperthermia

Cardiovascular causes

- Heart failure like due PDA
- Anemia
- Hypovolemia

Other causes

- Apnea of prematurity

Investigations

- Complete blood count (anemia, sepsis), blood culture and sensitivity
- Arterial blood gases
- Serum electrolytes, blood glucose, and calcium
- Cranial USG
- Echocardiography
- Chest X-ray

Management

- Infants at risk for apnea should get cardiorespiratory monitoring.
- Determine the cause of apnea and treat it if possible.
- Gentle tactile stimulation may be an adequate therapy for mild and intermittent episodes.
- Sepsis is a cause of apnea that cannot be overlooked because antibiotics need to be started. Make sure to rule out sepsis before treating other causes.
- General measures include :
  - Position the neck in slightly extended position.
  - Suck the oropharynx gently if required.
  - Providing tactile stimulation for neonates having mild and intermittent episodes.

  - Infants having recurrent and prolonged apnea require immediate bag and mask ventilation.
  - Oxygen should be administered to treat hypoxia. Airway should be kept patent.
  - Neutral thermal environment should be maintained.
- Apnea of prematurity not due to precipitating identifiable cause should be treated with methylxanthines (theophylline or caffeine).
  - These enhance ventilation through a central mechanism or by improving diaphragmatic strength.
  - Caffeine citrate (20 mg/kg as loading dose and then 5–10 mg/kg/d) is the drug of choice if available.
  - Loading doses of 5 mg/kg of theophylline PO or aminophylline IV should be followed by doses of 1–2 mg/kg given every 6–8 hours using oral or IV routes.
- Transfusion of packed red blood cells also may reduce the incidence of idiopathic apnea among severely anemic infants.
- Nasal Continuous Positive Airway Pressure (CPAP) is effective therapy to open airways for mixed or obstructive apneas.
- To prevent gastroesophageal reflux, keep the infant in the prone position (head up) as much as possible, and use small volume, thickened feedings.

Prognosis

- In most premature infants, apneic and bradycardiac spells are controlled by 34–37 weeks postconception.

NEONATAL SEPSIS

CASE

A 2-week-oldinfant presents with irritability, ***poor feeding***, ***fever*** and grunting. Physical examination reveals a ***bulging fontanel***, ***delayed capillary refill*** and ***tachypnea***.

Definition

- It is a clinical syndrome of systemic illness resulting from metabolic and circulatory collapse from infection in the newborn.
- It is bacterial infection in a neonate (in the first four weeks of life) that is documented by a positive blood culture.
- **Early onset sepsis** presents within first 3 days of life.
- **Late onset sepsis** occurs between 4 days of age up to one month of age.

Incidence

- Varies from 1–10/1000 live births and up to 22/1000 live births in developing countries.
- About 40% of neonatal deaths in Pakistan are due to sepsis.
- In Pakistan infant mortality rate is 78/1000 and perinatal mortality rate is 60/1000.
- Approximately one-third of septic newborns develop meningitis.

Predisposing factors

Host factors (i.e. in the newborn)

- Impaired cellular response:
  - The newborn is unable to adequately concentrate inflammatory cells at sites of inflammation. The leukocytes have defects in their response to chemotactic stimuli, in phagocytosis and show impaired bactericidal capacity.
- Impaired humoral response:
  - Only IgG is passively transferred from the mother to the newborn while IgM and IgA is not. This leaves the newborn with weak defenses if delivered prematurely.
  - Serum complement levels are low.
  - Bacteria adhere to intestinal epithelium because of lack of secretory IgA.

Maternal factors

- Poor socio-economic status (may be explained by LBW)
- Maternal illness at the time of labor and delivery (TLC >18000/ ☐)
- Intra-partum maternal fever of ≥38°C (100.4°F)
- Prolonged rupture of membranes (more than 18 hours)
- Maternal chorioamnionitis
- Prolonged labor (>18 hours)
- Maternal colonization (of cervix) with infectious agents (*E. coli, Group B streptococcus*)

CASE

Group B Streptococcus: A full term one week old infant presents with ***fever***, poor feeding, and a ***bulging fontanel***. Mother has history of prolonged rupture of membranes and a low-grade fever. Spinal fluid of infant demonstrates ***Gram-positive cocci***. Cerebrospinal fluid is turbid with 5500 WBC/mm^3 and a low glucose.

Environmental factors

- Home delivery
- Low birth weight
- Birth asphyxia
- Bacterial contamination at the time of labor and delivery
- Unclean hospital and nursery environment and practices (e.g. not washing hands properly, improper cord care)
- Prematurity (it is a single most significant factor correlated with sepsis)

- Bottle-feeding
- Indwelling venous or arterial catheters, endotracheal intubation, TPN, prolonged use of antibiotics

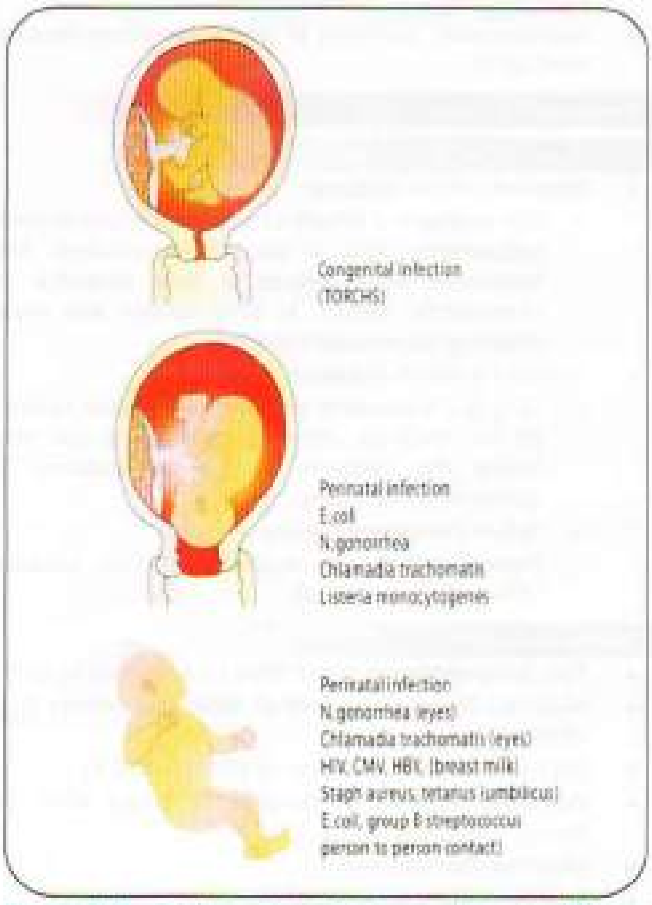

Congenital infection
(TORCHS)
Perinatal infection
E.coli
N.gonorrhea
Chlamadia trachomatis
Listeria monocytogenes
Perinatal infection
N.gonorrhea (eyes)
Chlamadia trachomatis (eyes)
HIV, CMV, HBV, (breast milk)
Staph aureus, tetanus (umbilicus)
E.coli, group B streptococcus
person to person contact)

Figure 9.12: Etiology of sepsis in newborn at different stages.

Etiology

- E. Coli
- Group B streptococcus
- Klebsiella
- Pseudomonas
- Staphylococcus
- Proteus

Clinical findings

- The early signs and symptoms of sepsis are non-specific.
- Generally the following should be sought:
  - Refusal to feed
  - Off color (does not look well)
  - Poor temperature control (fever, hypothermia) The normal neonatal isothermic temperature range is 97°F (36°C) to 99.6°F (37°C)
  - Poor peripheral perfusion, skin mottling, cold clammy skin, and cutis marmorata
  - Tachycardia or bradycardia
  - Inactivity, lethargy, hypotonia, full fontanel
  - Irritability, jitteriness, high pitch cry
  - Seizures, coma
  - Respiratory distress or apnea, cyanosis, flaring, grunting, retractions
  - Vomiting, diarrhea or distension increased aspirates, oliguria
  - Jaundice, purpura, petechiae, pallor, bleeding, hepatosplenomegaly
  - Impetigo, cellulitis, omphalitis, sclerema

Table 9.14: Initial signs and symptoms of infection in newborn infants.

General	Fever Temperature instability Poor feeding Edema
Neurologic	Irritability, lethargy Seizures Hypotonia Abnormal Moro reflex Irregular respirations Full fontanel
Respiratory	Apnea Tachypnea Retractions Flaring, grunting Cyanosis.
Cardiac	Pallor, mottling Cold skin Tachycardia Hypotension Bradycardia
Gastrointestinal	Abdominal distention Vomiting Diarrhea Hepatomegaly
Renal	Oliguria
Hematologic	Jaundice Splenomegaly Pallor Petechiae, purpura Bleeding

Investigations

Adjunctive tests

- The most reliable indicator is the peripheral white cell count (WBC count).
  - Abnormally elevated white cell count (>30,000/mm^3) or a low WBC count (<4,000/mm^3) is significant. Neutropenia (total neutrophil count <2000/mm^3) is a finding with poor prognosis when associated with sepsis.

  - A high proportion of immature neutrophils (>25%) or band-neutrophil ratio of 0.2 or higher is suggestive of sepsis.
- Low platelet count is suggestive (less than 150,000/mm^3).
- High ESR
- Abnormally raised value for C-reactive protein or Procalcitonin. These are acute phase reactant that increases in the presence of inflammation and infection.
- Chest X-ray; especially in infants with respiratory distress

Specific diagnostic tests

- **Blood culture:** Draw 1 ml/kg or at least 1ml blood by sterile technique (sensitivity 50–80%).
- **Cerebrospinal fluid culture.**
- **Urine culture** (it has little value in perinatal period, but may be very important for late-onset sepsis).
- **Tracheal aspirate** culture and gram stain may help to increase diagnostic accuracy of ventilator associated pneumonia (VAP)

Management

- It is preferable to get specimens for investigation of sepsis prior to the initiation of antimicrobial therapy.
- But, antimicrobial therapy administration should not be delayed even for specimen collection if the neonate is in serious condition.

Early onset sepsis

- Ampicillin + aminoglycoside (usually gentamicin) or cefotaxime are given.
- Ampicillin (100-300 mg/kg/day IV divided in 8 hourly doses).
- Gentamycin (5 mg/kg/day IV divided in 8-12 hourly doses).
- Ampicillin alone is adequate for *Listeria monocytogenes*.
- Penicillin alone is adequate for GBS.
- Clindamycin or metronidazole is appropriate for anaerobic infections.
- Duration of treatment is 10 days for bacteremia.
- Duration of treatment is 14 days for GBS and uncomplicated meningitis. It is extended to 21–28 days for complicated infections by gram negative pathogens
- Consider a third-generation cephalosporin (cefotaxime is preferred) or carbapenem for meningitis. Cefotaxime (100 mg/kg/day IV divided in 8–12 hourly doses).
- Therapy is changed according to the culture report.
- Carbapenem antibiotics are used in hospital acquired infections.

Late onset sepsis

- Vancomycin + aminoglycoside are given, especially in case of having long lines.
- Vancomycin (15 mg/kg/dose given 8 hourly).
- Amikacin (15 mg/kg/day divided in 12 hourly doses).
- Duration dependent on pathogen and site of infection.
- Alternatives to vancomycin may be considered according to culture report and clinical presentation.
- Consider cephalosporin if meningitis suspected.
- Consider a carbapenem if third-generation cephalosporin recently received.
- Ceftazidime or Carbapenem is given if *Pseudomonas* coverage is required.
- Amphotericin B is considered if fungal infection is present.

Supportive treatment

- Good temperature control. Maintenance of neutral thermal environment.
- Monitor vital signs.
- Strict intake and output record.
- Fluid and electrolyte balance (5% dextrose ½ normal saline then 1/5 saline).
- Good respiratory support with oxygen and artificial ventilation.
- Blood transfusion if baby is anemic (Hb <12 g/dl).
- Sodium bicarbonate 0.5-1ml/kg OF 8.4% preparation for metabolic acidosis.
- Monitor and manage metabolic disturbances especially serum electrolytes, hypoglycemia, hypocalcemia, and metabolic acidosis.
- Hyperbilirubinemia, if present, should be treated aggressively with antibiotics/or exchange transfusion, to avoid the risk of kernicterus (which increases in the presence of sepsis and meningitis).
- Seizures should be treated with anticonvulsants (e.g. phenobarbitone).
- Parenteral nutrition should be given to any infant who cannot tolerate enteral feeding.
- Steroids such as hydrocortisone 3 mg/kg/dose three times/day for refractory septic shock.
- Dopamine 7–15
- If bleeding occurs due to DIC, management is fresh-frozen plasma, platelet transfusions, or whole blood.
- Immunoglobulins such as Pentaglobin (highly enriched immunoglobulins IgM and IgG) or fresh frozen plasma can be given.
- GM-CSF (granulocyte-macrophage colony stimulating factor) in case of severe sepsis and neutropenia.

Complications of sepsis

- Endocarditis
- Septic emboli
- Abscess formation
- Septic joints with residual disability
- Osteomyelitis
- Bone destruction
- Recurrent bacteremia (rare <5% of patients)
- Candidemia

- Septic shock
- DIC
- Organ failure

Complications of neonatal meningitis

- Immediate complications of meningitis include ventriculitis, cerebritis, and brain abscess.
- Late complications of meningitis include hearing loss, abnormal behavior, developmental delay, cerebral palsy, focal motor disability, seizure disorders, and hydrocephalus.

Prevention

Hand washing

- Maternal vaccination against vaccine preventable diseases (rubella, VZV, hepatitis B, tetanus).
- Aggressive management of suspected maternal chorioamnionitis with antibiotic therapy. Early-onset group B streptococcal sepsis can be prevented by maternal intrapartum antibiotic prophylaxis.
- Breastfeeding and hand washing are helpful in prevention of late-onset sepsis.

Prognosis

- Case fatality rate varies from 20–50%.

TORCH INFECTIONS

- Many organisms can cross the placenta to cause fetal infection, and although severe neonatal symptoms may occur, intrauterine infections are frequently sub-clinical at birth.
- The term TORCH includes toxoplasmosis, others (such as syphilis, hepatitis B, etc.), rubella, cytomegalovirus and herpes simplex virus.
- This group of infections may present in the neonate with similar findings, i.e. small for gestational age, hepatosplenomegaly, rash, CNS manifestations, early jaundice, and low platelets.
- Neonate may present with following features if infected with TORCH infection:
    - Low birth weight
    - Jaundice, rash
    - Hepatosplenomegaly
    - Thrombocytopenia
    - Cataract
    - Chorioretinitis
    - Microcephaly
    - Congenital heart disease
- Some infants may be normal at birth but may develop deafness, mental defect and eye changes several years later.

TOXOPLASMOSIS

CASE

A newborn presents with ***hydrocephalus*** and ***chorioretinitis***. On CT scan, there are ***diffuse cerebral calcifications***.

- *Toxoplasma gondii* is a protozoan parasite capable of causing intrauterine infection.
- The incidence of congenital infections is 1 in 1000 to 1 in 10,000 live births.

Pathophysiology

- Newly infected cats excrete the infectious oocysts in their feces. *Toxoplasma gondii* may be ingested during contact with soil contaminated with cat feces. It may also be transmitted in unpasteurized milk and in raw or undercooked meats.
- The vast majority of congenital toxoplasmosis cases are a result of acquired maternal primary infection during pregnancy; however, toxoplasmic reactivation can occur in immuno-suppressed pregnant women and result in fetal infection.
- The later in pregnancy that infection is acquired, the more likely is transmission to the fetus.
- Infections transmitted earlier in gestation are likely to cause more severe fetal effects (abortion, stillbirth, severe disease with teratogenesis). Those transmitted later are more likely to be sub-clinical.
- 70–90% of infants with congenital infection are asymptomatic at birth. However, visual impairment, learning disabilities, or mental impairment becomes apparent months to several years later.

Clinical findings

- Obstructive hydrocephalus, chorioretinitis, and intracranial calcifications are the classic triad.
- The common clinical findings are microcephaly, microphthalmia, seizures, jaundice, rash, lymph-adenopathy, hepatosplenomegaly, thrombocytopenia, petechiae and fever.
- 70–90% of infants are asymptomatic at birth.

Investigations

- **Direct isolation of the organism from body fluids or tissues.** Isolation of organism from placental tissue correlates strongly with fetal infection.
- **Serologic tests:** A four-fold rise in antibody titer or seroconversion from negative to positive in mother indicates the presence of infection. If the maternal antibody status is negative, the diagnosis of congenital toxoplasmosis is excluded; if the maternal and neonatal levels are positive, serial studies for several months are necessary to distinguish transplacental antibody (levels will fall) from congenital infection (levels will remain stable or rise). Toxoplasma specific IgM antibodies usually become positive within 1–2

weeks of infection and persist for months. If IgM titers are high and accompanied by high specific IgG titers, this suggests acute infection. IgA antibodies are found in >95% of patients with acute infections. Toxoplasma specific IgE antibodies are found in almost all women who seroconvert during pregnancy.

- **Perinatal diagnosis** can be made by detecting the parasite in fetal blood or amniotic fluid, or by documenting Toxoplasma IgM and IgA antibodies in fetal blood. **Polymerase Chain Reaction** (PCR) detects its genomic material.
- **CSF examination:** The most characteristic abnormalities are xantho-chromia, mononuclear pleocytosis, and very high protein levels. Tests for CSF IgM to toxoplasmosis may also be performed.
- A **skull X-ray** or **CT scan** of the head may demonstrate characteristic intracranial calcifications (speckled throughout the CNS, including the meninges).
- **Ophthalmologic examination** shows chorioretinitis.

Treatment

- Pyrimethamine and sulfadiazine used in conjunction with folic acid.
- Spiramicin.
- Corticosteroids are reserved for patients with acute CNS or ocular infection.

Prevention

- Women should avoid eating raw meat or raw eggs and avoid exposure to the cat feces.

RUBELLA

CASE

An infant presents with ***growth and mental retardation***. At birth she had ***rash*** (bluish purpuric skin lesions) and ***absent red reflexes*** (cataracts). On auscultation, there is a ***heart murmur***.

- Rubella is a viral infection capable of causing chronic intrauterine infection and damage to the developing fetus.
- The incidence varies from 0.1% to 2% of births.

Pathophysiology

- The virus is acquired from infected respiratory secretions.
- Maternal viremia is a prerequisite for placental infection, which may or may not spread to the fetus.
- Maternal antibody to previous infection is protective for the fetus.
- Maternal infection during the first trimester results in fetal infection in more than 90% of cases.
- Women of childbearing age who are rubella nonimmune are at risk.

Clinical findings

- Main features are intrauterine growth retardation, microcephaly, microphthalmia, cataracts, glaucoma, chorioretinitis, hepatosplenomegaly, jaundice, PDA, pulmonary artery stenosis, sensorineural hearing loss, blueberry muffin rash, anemia, thrombocytopenia, leukopenia, metaphyseal lucencies, B-cell and T-cell deficiency.
- Infant may be asymptomatic at birth.
- Virus may be present in infant throat for 1 year.

Investigations

- **Cultures:** The virus can be cultured for up to 1 year despite measurable antibody titer. The best specimens for viral recovery are from nasal pharyngeal swabs, conjunctival scrapings, urine, and CSF.
- **CSF examination** may reveal encephalitis with an increased protein cellular ratio in some cases.

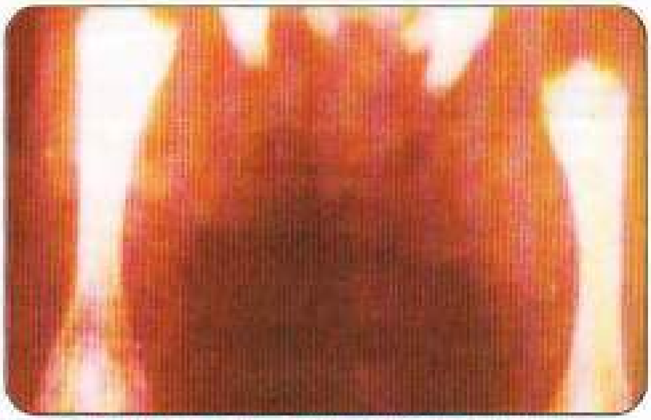


Figure 9.13: X-ray showing metaphyseal radiolucencies.

- **Serological studies:** congenital rubella also can be diagnosed in the neonatal period by the presence of a positive IgM antibody to rubella virus in the newborn's serum; increased IgM titer indicates recent rubella infection of the fetus, because IgM does not cross the placenta. There is persistence of rubella specific titers over time (i.e. no decline in titer as expected for transplacentally derived maternal IgG).
- **Radiological studies:** Long bone films may show metaphyseal radiolucencies that correlate with metaphyseal osteoporosis. This is caused by virus-induced inhibition of mitosis of bone-forming cells.

Treatment

- There is no specific treatment for rubella.
- Long-term follow-up is needed secondary to late-onset symptoms.

Prevention

- Vaccination of the susceptible population (especially young children). Vaccine should not be given to pregnant women.
- Infants with congenital rubella should be considered contagious until they are at least 1 year old, unless

nasophyryngeal and urine cultures are repeatedly negative for rubella virus.

CYTOMEGALOVIRUS (CMV)

CASE

A 7-month-old child presents with ***developmental delay***. He is not able to hold his neck. He was born at 38 weeks gestational age with 1.6 kg weight (***intrauterine growth retardation*** including ***microcephaly***). There was also ***hepatosplenomegaly, prolonged neonatal jaundice,*** and a ***generalized rash*** (blue-purple macules) at birth. On CT scan brain, there is ***periventricular calcifications***.

- CMV is a DNA virus and a member of the herpes virus group.
- It is the most commonly known human virus that is transmitted vertically to the fetus (transplacentally, during birth, and by breast milk).

Pathophysiology

- CMV may be transmitted in secretions, blood, and urine and perhaps by sexual contact.
- More than 90% of primary CMV infections are asymptomatic. Those with symptoms usually have a mononucleosis-like illness.
- Seroconversion and initial infection often occur around the time of puberty, and shedding of the virus may continue for a long time.
- CMV can also become latent and reactivate periodically. 10–30% of pregnant women have cervical colonization with CMV.
- CMV is capable of penetrating the placental barrier as well as the blood-brain barrier.
- Both primary and recurrent maternal CMV can lead to transmission of virus to the fetus.
- The period of greatest fetal risk for disease and subsequent neurologic impairment is the first 22 weeks of gestation.
- Infants with symptomatic disease usually are born to women with primary CMV infection. Symptomatic infants have a mortality rate of 20–30%.

Clinical findings

- Main features are sepsis, intrauterine growth retardation, chorioretinitis, microcephaly, periventricular calcifications, blueberry muffin rash, anemia, thrombocytopenia, neutropenia, hepatosplenomegaly, jaundice, abnormal LFTs, deafness, and pneumonia.
- Many are asymptomatic at birth.
- Infants may have viruria for 1–6 year.

Investigations

- **Culture** for demonstration of the virus: The gold standard for CMV diagnosis is urine or saliva culture.
- **Serological tests**: Negative IgG titers in both maternal and infant sera are sufficient to exclude congenital CMV infection. The interpretation of a positive IgG titer in the newborn is almost always complicated by the presence of transplacentally derived maternal IgG. Uninfected infants usually show a decline in IgG within 1 month and have no detectable titer by 4 to 9 months. Infected infants continue to produce IgG throughout the same time period. Tests for CMV-specific IgM have limitations but can help to elucidate infant infection.
- **Radiologic studies:** Skull films or CT scans of the head may demonstrate characteristic intracranial calcifications.

Treatment

- No treatment is required in asymptomatic or babies with mild mild symtptoms.
- Valganciclovir is used to treat CNS disease, significant organ involvement and in case of hearing loss.

Prevention

- Always transfuse CMV-negative blood products.
- Avoid breast feeding only if mother is postive and baby is asymptomatic and premature.

HERPES SIMPLEX VIRUS (HSV)

CASE

A 9-day-old full-term neonate presents with 1 day of ***vesicular lesions*** of the skin and mouth. He is afebrile and alert. There are multiple 3–5 mm vesicles on an erythematous base present on her trunk and mouth.

- HSV is a DNA virus.
- The estimated rate of occurrence of neonatal HSV is 1 in 1000 to 1 in 5000 deliveries per year.

Pathophysiology

- 3/4th of neonatal herpes infections are secondary to HSV-2, with the remainder caused by HSV-1.
- HSV infection of the neonate can be acquired intrauterine, intrapartum, or postnatal. Most infections (80%) are acquired in the intrapartum period as ascending infections with ruptured membranes or by delivery through an infected cervix or vagina.
- The usual portal of entry for the virus is the skin, eyes, mouth, and respiratory tract.
- Three general patterns of neonatal HSV are disease localized to:
  - Skin, eyes, and mouth
  - CNS
  - Disseminated disease
- 30–50% of infants born vaginally to mothers with a primary infection will themselves have HSV, compared

with only 3–5% of those born to mothers with recurrent infection.

- Maternal antibody is not necessarily protective in the fetus.

Clinical findings

- *Intrauterine infection:* Chorioretinitis, skin lesions, microcephaly
- *Postnatal:* Encephalitis localized or disseminated disease, skin vesicles, keratoconjunctivitis

Investigations

- **Viral cultures** are usually obtained from conjunctiva, throat, feces, urine, nasal pharynx, and CSF.
- **Immunologic assays** to detect HSV antigen in lesion scrapings, usually using monoclonal anti-HSV antibodies in either an ELISA or fluorescent microscopy assay, are very specific and 80–90% sensitive.
- **Tzanck smear:** Cytologic examination of the base of skin vesicles is with a Giemsa or Wright stain, looking for characteristic but nonspecific giant cells and eosinophilic intranuclear inclusions.
- **Serologic tests:** Serology is of little value, because specific IgM may not be detected for up to 3 weeks.
- **PCR** to detect HSV DNA is a very sensitive method. It can be very useful in detection of HSV in CSF in which cultures are often negative.
- **Lumber puncture** should be performed in all suspected cases. Evidence of hemorrhagic CNS infection with increased white and red blood cells and protein is found.
- **Radiologic studies:** CT scan or MRI of the head may be useful in the diagnosis of CNS disease.

Treatment

- The first-line drug of choice is acyclovir, the second choice being vidarabine.

Prevention

- Delivery by C-section in women who have clinically apparent HSV infection (particularly primary infection).
- Breast feeding is allowed unless herpetic lesions around nipple.

TUBERCULOSIS

- Congenital tuberculosis is rare.
- Women with only pulmonary infection usually do not infect their offspring until after birth.
- Clinical manifestations of congenital TB are mainly fever, failure to thrive, lethargy, irritability, hepatosplenomegaly and respiratory distress.
- If the mother's chest radiograph is abnormal but the history, physical examination, sputum examination, and evaluation of the radiograph shows no evidence of current active tuberculosis, it is reasonable to assume that the infant is at low risk for infection. The mother should receive appropriate treatment, and she and her infant should receive careful follow-up care. Mother should breast feed her baby. In addition, all household members should be evaluated for tuberculosis.
- If the mother's chest radiograph or acid-fast sputum smears shows evidence of current tuberculosis disease, INH therapy for newborn along with anti-tuberculous treatment of mother is started. INH treatment for the infant should be continued until the mother has been shown to be sputum culture negative for at least 3 months. At that time, a Mantous tuberculin skin test should be done on the infant along with X-ray chest. If positive, ATT is continued for a total duration of 6–9 months; if negative, INH is discontinued and BCG vaccination given. Breastfeeding is not contraindicated.

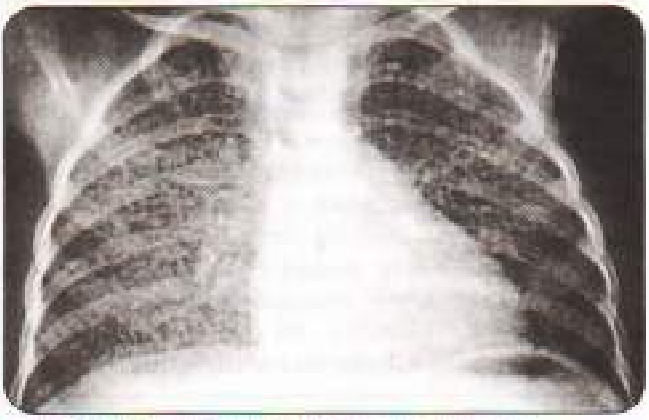


Figure 9.14: X-ray miliary tuberculosis in newborn.

- If congenital tuberculosis is suspected, multi-drug therapy should be immediately started. Skin test may not be positive for 6 months.

HEPATITIS B VIRUS

- The transmission of HBV from infected mothers to their newborns is thought to result primarily from exposure to maternal blood at the time of delivery. When acute maternal HBV infection occurs during the first and second trimesters of pregnancy, there generally is little risk to the newborns, because antigenemia is usually cleared by term and anti-HBs is present. Acute maternal HBV infection during late pregnancy or near the time of delivery, however, may result in a 50–75% transmission rate.
- It is recommended that all pregnant women be screened for HbsAg. All infants born to mothers confirmed to be positive for HBsAg should receive HBIG (0.5 ml IM) in addition to recombinant hepatitis B vaccine (0.5 ml) at a separate site. The first immunization and HBIG ideally should be given within the 12 hours of life and the vaccine is repeated at the ages of 1 and 6 months.
- There has been no documented increase in the risk of HBV transmission by breastfeeding mothers who are HbsAg positive. This is true even though HbsAg can be detected in breast milk.

JAUNDICE NEONATORUM

- Neonatal hyperbilirubinemia is a condition characterized by an excessive concentration of bilirubin in the blood.
- There are two types of hyperbilirubinemia:
  - **Unconjugated (Indirect)**, which can be physiological or pathological in origin.
  - **Conjugated (Direct)**, which is always due to pathological causes. Both types may lead to jaundice.
- Neurologic concentrations of unconjugated bilirubin can cause **kernicterus**.
- Jaundice is a common, and in most cases benign, neonatal problem. 60% of term and 80% of preterm newborns develop clinical jaundice with a bilirubin level above 5 mg/dl during the first week of life.

Normal bilirubin metabolism

- Jaundice is more common in newborns because of high hemoglobin mass (18–22 g/dl), and more than 75% is fetal hemoglobin, which is unstable at high oxygen tension and has short life span (60–70 days).
- Bilirubin is mainly derived from the breakdown of hemoglobin in the reticuloendothelial system. 1 g hemoglobin produces 34 mg bilirubin. Normal newborn has a bilirubin load of 18 mg/day.

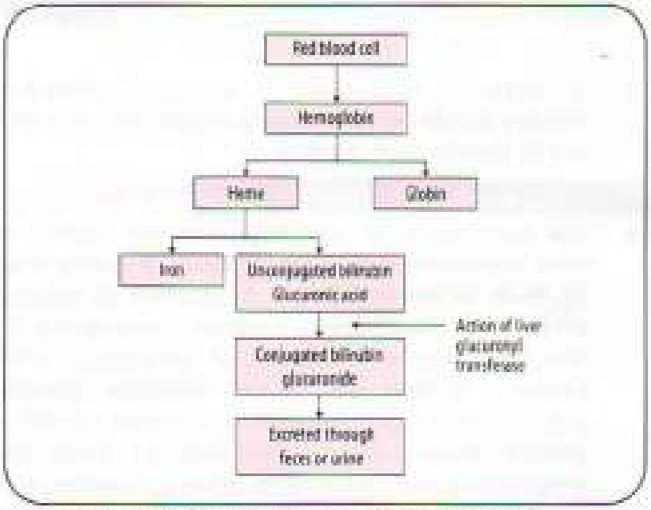

Red blood cell
Hemoglobin
Heme
Globin
Iron
Unconjugated bilirubin
Glucuronic acid
Action of liver glucuronyl transferase
Conjugated bilirubin glucuronide
Excreted through feces or urine

Figure 9.15: Formation and excretion of bilirubin.

- Hemoglobin is broken down into heme and globin by the enzyme heme oxygenase. Globin is used for further hemoglobin synthesis while heme is broken down into porphyrins. Cleavage of porphyrin ring yield biliverdin and CO. Biliverdin (green) is converted to bilirubin (yellow) by bilirubin reductase through a reduction reaction.
- Fat-soluble bilirubin (unconjugated bilirubin) normally circulates in plasma bound to albumin. Bilirubin bound to albumin does not usually enter the CNS and is thought to be nontoxic. Displacement of bilirubin from albumin by drugs (sulfonamides, ceftriaxone, vitamin K), or by free fatty acids may increase bilirubin toxicity. Albumin bound bilirubin is transported to hepatocytes. In the liver, conjugation with glucoronyl transferase converts bilirubin to a water-soluble product; conjugated bilirubin is excreted in bile (and also in urine). The enzyme activity can be enhanced by phenobarbitone.
- In the gut, bacteria cause deconjugation of the bilirubin and it is converted to urobilinogen and stercobilinogen. Some bilirubin is reabsorbed from the gut and enters the liver to be re-excreted in the bile (enterohepatic circulation). In general, a rise in unconjugated bilirubin is due to pre-hepatic causes. It occurs when there is an increased breakdown of the red blood cell (hemolysis), which exceeds the conjugating capacity of the liver. When the problem lies in the liver or its conjugating enzymes, there is usually a mixed picture of raised unconjugated and conjugated bilirubin. A predominant rise in conjugated bilirubin is usually due to interference with excretion of the bilirubin into the bile after conjugation. This will eventually be accompanied by a rise in unconjugated bilirubin.

UNCONJUGATED (INDIRECT) HYPERBILIRUBINEMIA

- Elevation of indirect serum bilirubin is related to bilirubin load minus bilirubin excretion and is therefore dependent on the gestational age and chronological age of the infant.

Etiology

- Unconjugated hyperbilirubinemia may occur because of increased bilirubin production (hemolysis), defective bilirubin clearance from the blood, or defective bilirubin conjugation by the liver.

Main causes

- Physiologic jaundice (most common cause)
- Hemolytic anemia
  - ABO or Rh incompatibility
  - G6PD deficiency
  - Infections (sepsis)
  - Drugs
  - Hereditary spherocytosis
- Polycythemia
  - Infant of diabetic mother
  - Postmaturity, SGA infants
  - Delayed cord clamping
  - Feto-maternal or feto-fetal transfusion
- Blood extravasation
  - Cephalhematoma
  - Bruises
- Breast milk and breastfeeding jaundice
- Glucuronyl transferase defect
  - Crigler Najjar syndrome (type I and II)
  - Gilbert syndrome
- Metabolic disorders

  - Galactosemia
  - Hypothyroidism
- Increased enterohepatic circulation
  - Ileus, intestinal obstruction
  - Pyloric stenosis

PHYSIOLOGIC JAUNDICE

CASE

A 3-day-old term, ***healthy infant*** presents with ***jaundice.*** On physical examination he is alert and normal. On laboratory investigations, hemoglobin is 16 g/dL, reticulocytes 1.0%, bilirubin ***unconjugated*** 8.5 mg/dL (***raised***), ***conjugated*** 0.8 mg/dL (***normal***).

Definition

- It is a diagnosis of exclusion, having the following criteria:
  - It occurs in apparently healthy infants.
  - Clinical jaundice appears after 24 hours of age.
  - Total bilirubin rises by less than 5 mg/dl/day.
  - Peak bilirubin occurs at 3–5 days of age, with a total bilirubin of no more than 12.9 mg/dl in term and more than 15 mg/dl in preterm infant.
  - Clinical jaundice is resolved by 1 week in the term and 2 weeks in the preterm infant.
- Hyperbilirubinemia outside of these criteria, or jaundice that requires treatment, is not physiologic and must be further evaluated.

Mechanisms of physiologic jaundice

- Increased bilirubin load because of the larger red blood cell volume, the shorter life span of the red blood cells, and increased enterohepatic circulation in newborn infants
- Defective uptake of bilirubin by the liver
- Overall impairment of liver function

HEMOLYTIC DISEASE OF THE NEWBORN

- **Acquired** hemolytic anemia may be seen in ABO or Rh incompatibility (e.g. erythroblastosis fetalis) between infant and mother. It may also be associated with the use of certain drugs (e.g. sulfonamides) or with infections.
- Hemolytic anemia may result from a **congenital** red blood cell defect such as hereditary spherocytosis, G6PD deficiency.

Rh Incompatibility

CASE

A ***full term baby*** presents with ***pallor*** and ***jaundice*** at 2nd day of life. Mother's first baby did not have jaundice at birth. On clinical investigations, ***direct Coombs test*** is ***positive***. Mother's blood group is ***Anegative***. Baby's blood group is O***positive***.

- It is responsible for 6/1000 births with hemolytic disease of newborn due to incompatibility of the maternal and fetal rhesus groups.
- The mother is Rh-negative and fetus is Rh-positive.
- Some fetal RBCs cross the placenta and enter the maternal circulation by a minor tear or at the time of delivery. These fetal red cells sensitize the mother to antigens on the surface of fetal red cells causing synthesis of anti-D IgM and IgG antibodies.
- IgG antibodies are not usually produced on first exposure to an antigen, but require initial sensitization, an amplified response on second or subsequent exposure. Thus, significant rhesus hemolytic disease is uncommon in first pregnancy, but increased in incidence and severity with increasing parity.
- The IgG antibodies can cross the placenta and forms complex with fetal red cells causing hemolysis in the spleen leading to anemia and jaundice. The earlier the antibody crosses the fetus, the more severe the disease.
- Hemolysis starting in the 2nd trimester may cause severe anemia with hepatosplenomegaly, liver damage, and hypoprotienemia, cardiac failure and generalized edema with ascites (hydrops fetalis). When hemolysis starts near to term, the infant is born with moderate anemia but develops neonatal jaundice, which may be severe.
- Major blood group (ABO) incompatibility protects the newborn from developing Rh incompatibility as fetal cells entering maternal circulation are destroyed by naturally occurring anti-A or B antibodies before they have time to sensitize Rh system (the IgG antibody is responsible for positive coomb's test). Rh incompatibility may present in the form of abortion, severe jaundice, mild anemia, hydrops fetalis or death.

ABO Incompatibility

CASE

A newborn baby presents with history of ***jaundice*** at ***3rd day of birth***. Mother's blood group is ***O*** positive and newborn baby's blood group is ***A*** positive. Serum bilirubin level is 15 mg/dL which is mainly unconjugated. ***Direct Coombs test is positive***. Mother's first baby also had history of jaundice at birth.

- ABO incompatibility is present in 20–25% of pregnancies but hemolytic disease is present in only 1 in 10 of such pregnancies. In this case the mother's blood group is usually type O and infant is A or B.
- Severe form of hemolysis is rare in these patients. There are several reasons for this:
  - The naturally occurring ABO antibodies are IgM rather than IgG and, therefore, do not cross the placenta.

  - Fetal A and B antigens are weak and produce little antibody response in the mother.
  - Any antibody produced by the mother may be neutralized by soluble A or B group substance or by the fetal tissue antigens.
- Mothers with blood group O are more likely to have IgG antibodies, which cross the placenta.
- Direct coomb's test may be negative because of low antibody titers.
- ABO hemolytic disease may be seen even in the first-born infants.
- Following combinations may occur:

Table 9.12: Possible hemolytic combinations.

Mother	Infant
O	A, B or AB
A	B or AB
B	A or AB
AB	No incompatibility

Other forms

- Minor groups' (Kell, Kidd, Duffy, Diego, etc.) incompatibility is responsible for 5% cases of jaundice.

Clinical features/evaluation

- In Rh or ABO incompatibility, infants are apparently born normal but jaundice manifests within a few hours after birth.
- The following points in the history and examination may help to know and evaluate the causes of jaundice neonatorum.
- A **family history** of jaundice, anemia, or metabolic disorder is significant. A history of a previous sibling with jaundice may suggest blood group incompatibility, breast milk jaundice, or G6PD deficiency.
- **Maternal history:** Risk of neonatal jaundice is increased with a history of maternal diabetes or infection. Use of oxytocin, sulfonamides, antimalarials, and nitrofurantoins by the mother may initiate hemolysis in G6PD deficient infant. Birth trauma, asphyxia, delayed cord clamping, and prematurity are associated with an increased risk of hyperbilirubinemia in the infant.
- **Infant's history:** Factors associated with gastrointestinal tract may affect the bilirubin level. Poor breastfeeding or poor caloric intake by the infant may increase the enterohepatic circulation of bilirubin and thus jaundice. Vomiting may be an early presentation in sepsis, intestinal obstruction, or metabolic disorders, all of which may increase the risk of bilirubin load and toxicity. Delayed passage of meconium and infrequent stooling are seen with intestinal obstruction.
- **Symptoms and signs:** Jaundice should always be seen in daylight; also examine the colour of urine and stool. Clinical jaundice is visible when the serum bilirubin level approaches 5–7 mg/dl. Jaundice is often apparent first in the face, especially the nose, then descending to the trunk and lower extremities as the degree of jaundice increases. Jaundice can be demonstrated in some infants by pressing lightly on the skin with a finger. The yellow color is seen more easily in the pressure area than in the surrounding skin. These signs should not appear within the first 24 hours after birth in otherwise healthy infants. Besides confirming the presence of jaundice, physical examination may also be helpful in determining the cause of hyperbilirubinemia. Areas of bleeding such as cephalhematoma, petechiae, or ecchymoses indicate blood extravasation. Hepatosplenomegaly may signify hemolytic disease, liver disease, or infection. Physical signs of prematurity, IUGR, postmaturity may be helpful to find a cause of hyperbilirubinemia. Plethora is seen with polycythemia, pallor with hemolytic disease, and large infants with maternal diabetes (all are associated with hyperbilirubinemia). Omphalitis, chorioretinitis, microcephaly, and petechial and purpuric lesions all suggest infectious causes of increased serum bilirubin.
- The appearance of abnormal **neurologic signs** shows the onset of early bilirubin encephalopathy.

Investigations

1. Hyperbilirubinemia should be investigated whenever pathologic causes are suspected.

Four basic investigations are

1. Serum bilirubin levels (total, direct, indirect):
2. Complete blood cell count and reticulocyte count:
   - Hemolytic anemia can be detected by a low hemoglobin or hematocrit associated with a high reticulocyte count and the presence of nucleated red blood cells.
   - Total WBC count with differential and platelet count may help detect sepsis.
   - Polycythemia is defined as a venous blood hematocrit >65%.
   - The peripheral blood film help in the diagnosis of hereditary spherocytosis and other red cell defect.
3. Blood groups of mother and baby:
   - ABO and Rh incompatibility can be easily diagnosed by comparing infant and maternal blood group types.
4. Direct Coomb's test in the infant:
   - The direct coomb's test is usually positive in isoimmunization disorders.

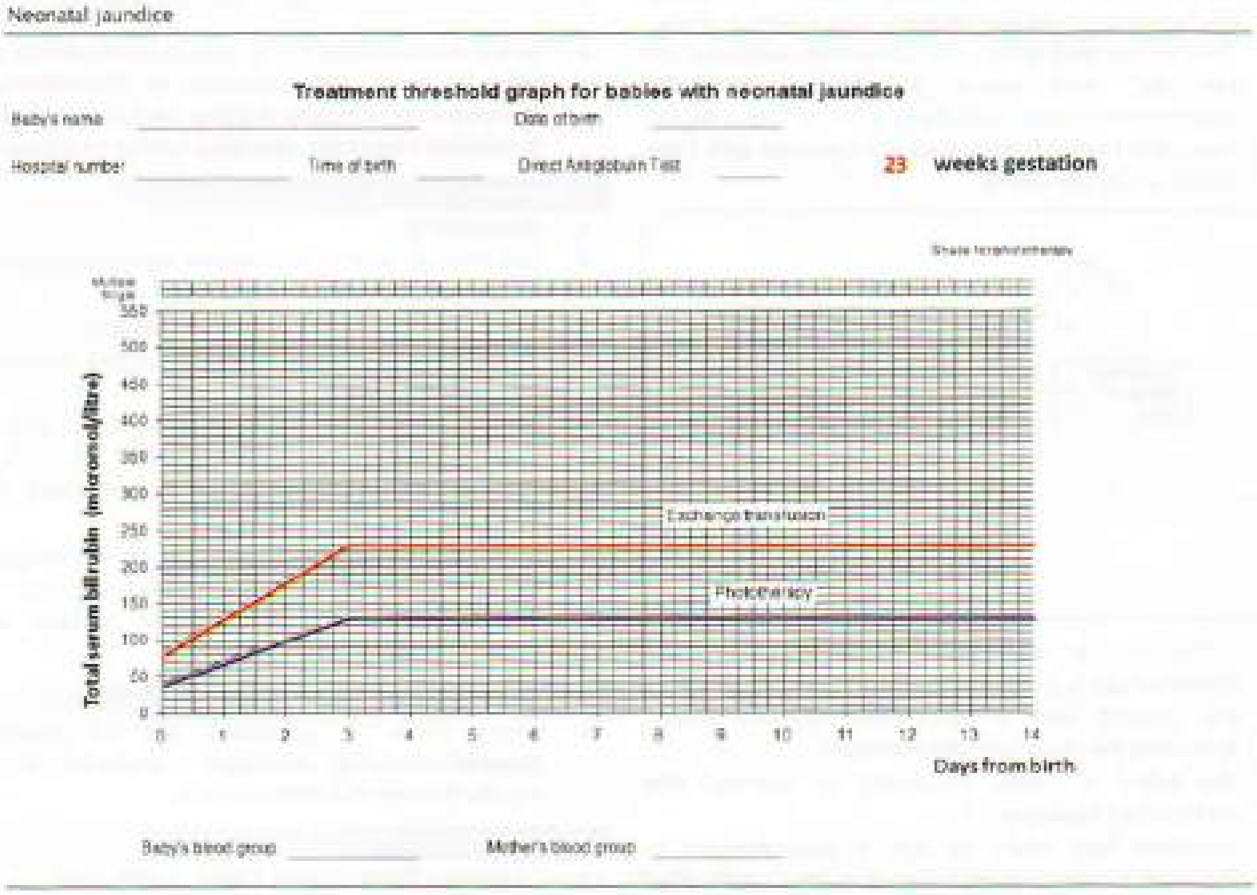
Secondary tests

- Blood culture
- Complete urine examination

- Liver function tests
- TORCH antibody titer
- G6PD enzyme assay
- Abdominal USG
- HIDA scan
- Urine examination for reducing substances
- Liver biopsy

Management

- Regardless of the cause, the goal of therapy is to prevent neurotoxicity related to indirect-reacting bilirubin. The results of total serum bilirubin should be plotted and managed on normgram/graph in line with baby,s postnatal age in hours or in accordance with times specific value on the threshold. These graphs are available on NICE guidelines website https://www.nice.org.uk/guidance/cg98/evidence/full-guideline-245411821



Neonatal jaundice

Treatment threshold graph for babies with neonatal jaundice

Baby's name ______ Date of birth ______

Hospital number ______ Time of birth ______ Direct Antiglobulin Test ______ 23 weeks gestation

Baby's blood group ______ Mother's blood group ______

- Three main methods are commonly used to decrease the level of unconjugated bilirubin.
  1. Phototherapy
  2. Exchange transfusion
  3. Pharmacologic therapy

Phototherapy

Indications

- When bilirubin is about 5 mg below the exchange level and mainly hemolytic.
- When serum bilirubin is unconjugated.
- In hemolytic disease of the newborn during the wait for exchange transfusion.
- Following the exchange transfusion to prevent further rise.
- Prophylactic phototherapy may be indicated:
  - In extremely low birth weight infants
  - In severely bruised infants

Mechanism

- Infants with unconjugated hyperbilirubinemia are exposed to blue light of phototherapy. Bilirubin absorbs light maximally in the blue range (420–470 nm).
- The light energy enhances the degradation of toxic unconjugated bilirubin (4Z, 15Z isomers) in the skin to non-toxic unconjugated bilirubin (4Z, 15E), which is excreted in the bile and does not need any conjugation by the liver. Bilirubin is also converted to lumirubicin (non-toxic) and to other water-soluble by-products

(bipyrrole, bilichrysin and hydroxyrubicin) all of which are readily excreted in the urine by the kidney.

- Two types of phototherapy devices are in use 1) conventional and 2) fibreoptic. Conventional ones include fluorescent lamps, quartz halogen lights and gas discharging rods. They have the advantage of being inexpensive but their light intensity and irradiance reduces with time, needing service with replacement of bulbs after approximately 2000 hours17. Phototherapy can also be given by fibreoptic systems via a baby pad or a wrap. Newer generation phototherapy units use multiple light emitting diodes. They do not emit infrared or ultraviolet radiations and can be used closer to infant's skin for maximumirradiance. LEDs have a life of about 60,000 hours and their intensity does not decrease with time, hence are longer lasting

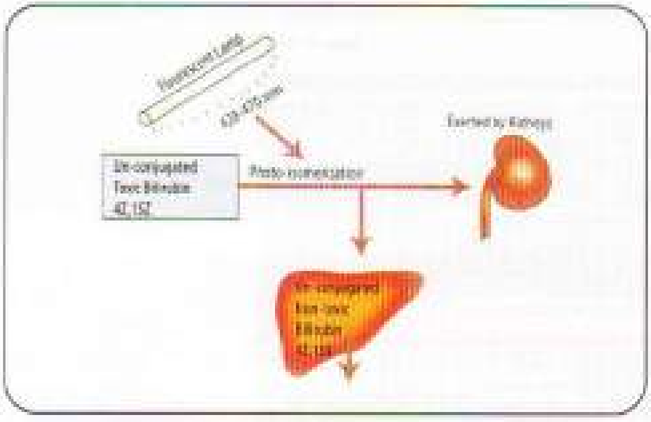


Figure 9.16: Mechanism of phototherapy.

- Phototherapy is given continuously. Only infant's eyes are covered with a patch and they are turned frequently for maximum skin exposure.
- The infant is turned frequently for maximal skin surface area exposure.
- Increased fluid intake by 30% is recommended to replenish evaporative water losses in old phototherapy units.
- Bilirubin level should be monitored at least every 12–24 hours. Allow infants to be removed from phototherapy for feeding.
- Aggressive phototherapy may improve neurodevelopmental outcome in infants <1,000 g.

Duration of phototherapy

- Phototherapy is stopped when the following criteria are met:
    - The bilirubin level is low i.e 3mg/dl lower than phototherapy level, enough to eliminate the risk of kernicterus.
    - The risk factors for the infant have resolved.
    - The infant is old enough to handle the bilirubin load.

Figure 9.17: A newborn baby under phototherapy machine.

- Serum bilirubin monitoring should be continued for at least 24 hours after cessation of phototherapy in patients with hemolytic disease, because sudden rises in bilirubin may occur, requiring further treatment.

Complications

- Overheating
- Dehydration (due to overheating and insensible water loss) in old phototherapy units.
- Hypothermia and chilling (winter months)
- Skin rashes (associated with transient increase in porphyrinemia)
- Loose stools (due to increased bile salts and unconjugated bilirubin in the bowel)
- Eye injury (corneal abrasion and conjunctivitis), retinal damage
- Bronze baby syndrome: When infants with conjugated hyperbilirubinemia are given phototherapy, they develop dark brown discoloration of skin, which persists for many months

Exchange transfusion

- When there is significant risk of developing hyperbilirubinemia, exchange transfusion is done usually through the umbilical vein.

Aims

- To remove the sensitized RBCs
- To remove the circulating antibodies
- To remove the circulating bilirubin
- To improve the anemia

Indications

At birth (cord blood)

- Hemoglobin below 12 g/dl
- Serum bilirubin above 5 mg/dl
- Coomb's test is positive
- Reticulocyte count above 10%

1st week

- If serum bilirubin is above the threshold of exchange transfusion in accordance with gestational age and postnatal days in NICE graphs.
- Previous history of exchange transfusion, kernicterus or death due to neonatal jaundice in a sibling.

- In a premature low birth weight baby, bilirubin level reaching 10–15 mg/dl.
- When phototherapy fails to prevent a rise in bilirubin to toxic levels, and bilirubin level is rising over 1 mg/dl/hour despite phototherapy.
- There is progression of anemia in the face of adequate control of bilirubin by other methods (e.g. phototherapy).

Equipment: (These should be sterilized)

- Sterile towels (two), artery forceps (six), sponge forceps, tooth forceps, scalpel blade, gauze pieces, umbilical catheter or NG tube no. 6, three way stop cock (two), disposable syringes 30 ml (two), exchange transfusion record sheet.

Site

- Umbilical vein (single, thin walled, large lumen, dark in colour)
- Umbilical artery (two, thick walled, small lumen, pink in colour)
- Large peripheral vein (jugular or saphenous)

Blood type

- Use fresh (<5 days old) blood, stored in citrated phosphate dextrose.
- In hemolytic disease, if blood is prepared before delivery, it should be type O Rh-negative cross-matched against the mother. If the blood is arranged after delivery, it also may be cross-matched against the infant.
- In ABO incompatibility, the blood should be type O Rh-negative or Rh-compatible with the mother and infant, cross-matched against mother and infant, and have a low titer of naturally occurring anti-A or anti-B antibodies. Type O cells may be used with AB plasma to ensure that no anti-A or anti-B antibodies are present.
- In case of Rh incompatibility blood for transfusion should be of baby's ABO and mother's Rh group.
- Subsequent exchange: complete cross match and direct Coomb's test.
- Now a days , there is practice of component therapy i.e packed RBCs.If exchange transfusion is planned in that case,then AB blood group FFP should be used before and in the middle of exchange transfusion with 10ml/kg dosage.

Infant's preparation

- Properly drape the baby
- Empty the stomach by N/G tube aspiration
- Maintain temperature by the use of baby warmer,respiration and heart rate
- *Cut umbilical cord near the stump*
- Identify umbilical vein and insert the catheter under strict asepsis
- Flush the catheter and syringes with heparin

Procedure

- Infants requiring exchange transfusion need wet umbilical stump, which is soaked continuously with gauze piece for cannulation of umbilical vein. Amount of blood required is twice the infant's blood volume, i.e. 160 ml/kg. The catheter is advanced just beyond the umbilical vein, avoiding advancing it to the liver.
- Blood is withdrawn in aliquots of 10–20 ml from the baby depending upon baby weight, discarded with the help of the three-way stopcock, fresh 10–20 ml drawn from the blood bag and introduced into the baby. There is no role of calcium gluconate infusion during or after exchange transfusion.

Complications

- Hypervolemia due to circulatory overload
- Hypothermia due to exposure during winter months
- Reactions due to blood group incompatibilities
- Vomiting and aspiration if stomach is not empty
- Cardiac arrhythmias or arrest
- Hypocalcemia
- Hyperkalemia (if blood of more than 5 days old is used)
- Infections, e.g. ascending cholangitis, septicemia, or hepatitis
- Air embolism
- Portal vein thrombosis
- Necrotizing enterocolitis
- Anemia if blood with low hemoglobin is given
- Failure of phototherapy is defined as failure of the bilirubin level to stabilize or decline by at least 1 to 2 mg/dl within 4–6 hours in infants exposed to intensive phototherapy.

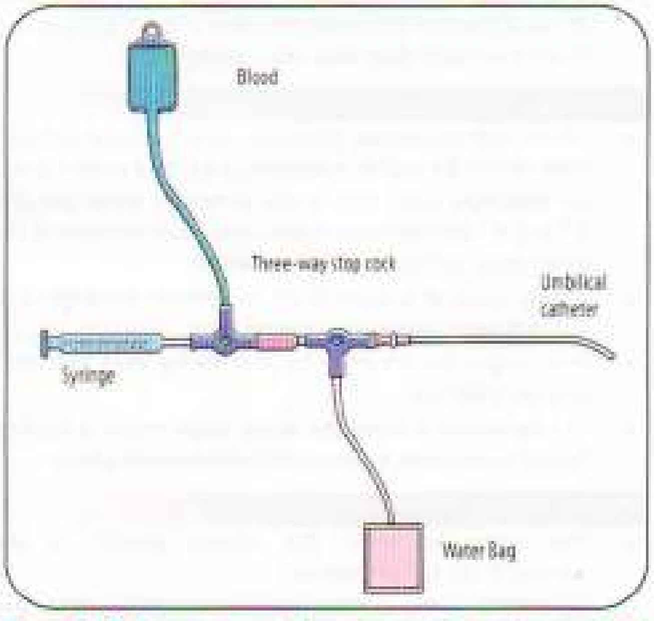


Figure 9.18: Arrangement of equipment for exchange blood transfusion.

General measures and pharmacologic therapy

- Give antibiotics if septicemia is present.

- Give adequate feeding.
- Prevent Rhisoimmunization in the mother by giving Rh$_0$ (D) immune globulin (Rhogam) injection within 72 hours of delivery of Rh positive infants.

Metalloporphyrins

- Metalloporphyrins are heme oxygenase inhibitors and so they decrease bilirubin production.
- A single intramuscular dose on the 1st day of life may reduce the need for phototherapy.

Intravenous immunoglobulin

- A 0.5–1.0 g/kg/dose of intravenous immunoglobulin (IVIG) given to the infant as soon with the diagnosis of ABO or Rh hemolytic disease is made has been shown to decrease the need for exchange transfusion. It reduces the hemolysis. It may be repeated in 12 hours.More helpful in those cases where bilirubin level is increasing despite intensive phototherapy and you are preparing for exchange transfusion.

KERNICTERUS (BILIRUBIN ENCEPHALOPATHY)

CASE

Full term 7-day-old baby presents with history of ***jaundice*** since 2nd day of his life. Now, he is ***lethargic*** with ***poor feeding***. On clinical examination, he has ***poor Moro response, deep jaundice***and opisthotonic posture.

- Kernicterus occurs in about 30% of infants with bilirubin levels >25–30 mg/dl.

Definition

- It is a neurologic syndrome resulting from deposition of unconjugated (indirect) bilirubin in basal ganglia and brain stem cells (bilirubin neuropathy).

Pathology

- When indirect serum bilirubin, which is lipid soluble, rises above 20 mg/dl, it crosses the blood brain barrier (in neonates only) and stains generally basal ganglia, 3rd and 8th cranial nerve nuclei and other centers of the brain deep yellow (nuclear jaundice).
- It may occur at a lower level in preterm neonate or in sick full-term (asphyxia, acidosis, etc).
- It damages the neurons by interfering with oxidative phosphorylation.
- In infants who survive the acute stage, there is marked loss of nerve cells followed by replacement gliosis.

Clinical findings

- The more immature the infant, greater is the susceptibility to kernicterus.
- In infants with kernicterus neurological signs are predominant.
- Acute Bilirubin Encephalopathy
- There is fairly sudden onset of lethargy and poor feeding in an infant with deep jaundice. There is weak or absent Moro reflex, high-pitched cry with increased muscle tone and head retraction (opisthotonus).
- Apnea, respiratory irregularity and convulsions occur. Usually there is up rolling of the eyeballs and constant tongue protrusion occurs.
- Majority of children die but those who survive show during the first year muscular rigidity, opisthotonus and convulsions.
- Chronic Bilirubin Encepalopathy
- Later in the 2nd or 3rd year of life complete neurologic syndrome develops in which there is bilateral choreoathetosis, extrapyramidal signs, high tone deafness, squints, seizures and mental retardation.
- Death occurs from respiratory failure, progressive coma or intractable seizures.

Prevention

- Once kernicterus develops it is irreversible.
- It can only be prevented by intensive phototherapy or exchange transfusions (by preventing the bilirubin level rising above the dangerous levels).
- Albumin infusion 1 gm/kg for hypoalbuminemia or IVIG (intravenous immunoglobulins) for ABO sensitization may be helpful.
- Follow up until school age is necessary for extra-pyramidal function and auditory function.

BREAST MILK JAUNDICE

- It is late onset unconjugated hyperbilirubinemia due to an inhibitor of conjugation (glucuronidase) present in the breast milk of some mothers.
- Breast milk jaundice develops in about 2% of breastfed term infants.
- Hyperbilirubinemia peaks at 7th day of age, with a maximal level of 10–30 mg/dl at 2nd–3rd weeks of age, and then bilirubin level slowly falls but may persist for 3–10 weeks of age at lower levels.
- If the breastfeeding is stopped, the bilirubin level will fall rapidly in 48 hours, and will not rebound to the same level when breastfeeding is restarted.
- Phototherapy may help lower the bilirubin levels.
- Kernicterus is an uncommon complication.

BREASTFEEDING JAUNDICE

- It,s misnomer, actual name should be breast not feeding jaundice.
- Breastfeeding jaundice (>12 mg/dl) is unconjugated hyperbilirubinemia (occurs during 1st week after birth) due to dehydration (decreased milk intake).
- It develops in about 13% of breastfed infants.
- Treatment is with increasing breastfeeding (>10 times/day) or adding formula milk.

Signs of Inadequate Breast Milk Intake

- Weight loss of >8–10% from birth.
- Fewer than six noticeably wet diapers per 24 hour by day 3–4.

- Fewer than four stools per day, or still meconium, by day 3–4.
- Nursing fewer than eight times per 24 hour, or for less than 10 minutes each feeding.

PERSISTENT JAUNDICE

- It is defined as jaundice persisting for more than 2 weeks.

Significant Causes

- Prematurity
- Breast milk jaundice
- Hypothyroidism
- Down syndrome
- Galactosemia
- Crigler-Najjar syndrome
- Pyloric stenosis or bowel obstruction
- Neonatal hepatitis, biliary atresia

PATHOLOGIC JAUNDICE

CASE

A full term, normal birth weight infant presents at the ***age of one month***. His jaundice is increasing from first week of life. He is passing ***pale stools***. There is ***hepatomegaly***, elevated ***conjugated bilirubin*** and raised LFTs (liver function tests).

- Jaundice is pathological (non-physiologic) if:
  - It is evident on the 1st day of life.
  - Bilirubin level increases more than 5 mg/dl/day.
  - Peak bilirubin is greater than 12 mg/dl in term infant or 15 mg/dl in preterm infant.
  - Direct bilirubin fraction is greater than 2 mg/dl at any time.
  - Jaundice persists after 14 days after birth.
- Other factors suggesting a non-physiologic cause of jaundice are:
  - Family history of hemolytic disease
  - Pallor (anemia)
  - Hepatomegaly
  - Splenomegaly
  - Failure of phototherapy to lower the bilirubin level
  - Apnea, bradycardia, hypothermia
  - Vomiting, lethargy, poor feeding, weight loss (sepsis or metabolic disease)
  - Light-colored stools
  - Dark urine positive for bilirubin
  - Kernicterus.

Causes of pathologic unconjugated Hyperbilirubinemia

a. Overproduction of bilirubin

Hemolytic causes of increased bilirubin production (reticulocyte count elevated)

- ABO blood group incompatibility, Rh incompatibility, minor blood group incompatibility
- Abnormal red cell shapes (spherocytosis, elliptocytosis, pyknocytosis, stomatocytosis)
- Red cell enzyme abnormalities (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency, hexokinase deficiency, other metabolic defects)
- Patients with bacterial or viral sepsis

Nonhemolytic causes of increased bilirubin production (reticulocyte count normal)

- Extravascular hemorrhage (cephalohematoma, extensive bruising, intracranial hemorrhage)
- Polycythemia
- Exaggerated enterohepatic circulation of bilirubin (bowel obstruction, functional ileus)
- Breast milk jaundice

b. Decreased rate of conjugation

- Crigler-Najjar syndrome (glucuronyl transferase deficiency)
- Gilbert syndrome
- Hypothyroidism

CONJUGATED (DIRECT) HYPERBILIRUBINEMIA

- Conjugated hyperbilirubinemia is defined as the direct bilirubin level >2.0 mg/dl or greater than 20% of the total serum bilirubin. .
- It is always pathologic
- Conjugated hyperbilirubinemia is a sign of hepatobiliary dysfunction.
- It results from a defect or insufficiency in bile secretion, biliary flow, or both.
- Thus there is an inability to remove conjugated bilirubin from the body.
- Conjugated hyperbilirubinemia usually appears in the newborn infant after the first week of life, when the indirect hyperbilirubinemia of physiologic jaundice has receded.
- It may be associated with hepatomegaly, splenomegaly, pale stools, and dark urine.

Causes

- Bile flow obstruction:
  - Biliary atresia
  - Choledochal cyst
  - Stenosis of the bile duct
  - Inspissated bile syndrome
  - Cystic fibrosis
- Liver cell injury:
  - Infections (sepsis, hepatitis, TORCH infections)
  - Metabolic (galactosemia, fructosemia, storage diseases, α_1-antitrypsin deficiency)
  - Toxic (due to TPN induced cholestasis)
  - Genetic disorders (Dubin-Johnson syndrome, Rotor's syndrome)

Investigations

- Investigations are selected according to the suspected cause of conjugated hyperbilirubinemia
- Bilirubin levels (total, direct, indirect)
- Liver function tests: SGOT (AST), SGPT (ALT), alkaline phosphatase
- Complete blood count, hemoglobin, and reticulocyte count
- Culture of blood, urine, spinal fluid
- TORCH antibody titers
- HBsAg status
- Metabolic screening of blood and urine
- Abdominal USG (to view liver parenchyma and to diagnose dilatation of the biliary tree)
- HIDA scan
- Percutaneous liver biopsy

Management

- Management depends on the cause of conjugated hyperbilirubinemia.
- Sepsis is treated with appropriate antibiotics.
- In cholestatic jaundice, promotion of bile flow and prevention of malnutrition, vitamin deficiencies, and bleeding are goals of treatment.
- Phenobarbitone and cholestyramine will promote bile flow and decrease serum bilirubin and bile salt levels.
- In case of biliary atresia, attempts should be made to establish biliary drainage with the use of hepatic porto-enterostomy (the Kasai procedure) before 6-8 weeks of age.
- TPN-induced conjugated hyperbilirubinemia will usually resolve once TPN is stopped.
- In cases where no treatment is curative or available, liver transplantation may be considered for end-stage liver disease.

POST-TERM INFANT

Definition

- A post-term infant is born after 42 weeks of gestation, calculated from the mother's last menstrual period, regardless of weight at birth.

Etiology

- In most cases, cause is not known.
- Anencephaly
- Trisomies 16 and 18
- Seckel's syndrome

Clinical findings

- Post-term infants are characterized by:
    - The absence of lanugo
    - Decreased or absent vernix caseosa
    - Long nails
    - Abundant scalp hair
    - White scaly, desquamating, loose wrinkled skin
    - Increased alertness.
- If placental insufficiency occurs, the amniotic fluid and fetus may be meconium stained, and the infant may be growth retarded.

Complications

- Meconium aspiration
- Hypoglycemia
- Hypocalcemia
- Birth asphyxia
- Polycythemia

Management

- Careful obstetric monitoring may help to decide the time and mode of delivery. Induction of labor or cesarean section may be indicated in older primigravidas who go more than 2–4 weeks beyond term especially if there is fetal distress.
- Early feeding for proper nutritional support is important.
- Meconium aspiration pneumonia or hypoxic ischemic encephalopathy is treated symptomatically.

Prognosis

- There is a significant increase in mortality when delivery is delayed 3 weeks or more beyond term.
- Improved obstetric management may lower mortality.

LARGE FOR GESTATIONAL AGE (LGA) INFANT

Definition

- The newborn is called LGA if birth weight is 2 standard deviation above the mean *OR*above the 90th percentile.

Etiology

- Constitutionally large infants are of large parents.
- Infants of diabetic mothers.
- Beckwith-Wiedmann syndrome.
- Some post-term infants.
- Infants with transposition of the great arteries (TGA).
- Erythroblastosis fetalis.

Complications

- Birth asphyxia.
- Birth trauma (fractured clavicle, Erb's palsy).
- Hypoglycemia.
- Polycythemia.

Management

- Infants should be evaluated for above complications and managed appropriately.
- Hypoglycemia should be monitored.
- The infant should be fed early because some LGA infants have hyperinsulinism (IDM, erythroblastosis fetalis, Beckwith-Wiedmann syndrome) and so are prone to hypoglycemia.

SMALL FOR GESTATIONAL AGE INFANT (S

Definition

- According to WHO Small for Gestational Age is defined as baby whose birth weight is less than the 10th centile for his gestation or more than 2 standard deviation below the mean for gestation.

Incidence

- About 3–10% of all pregnancies are associated with intrauterine growth retardation (IUGR), and 20% of stillborn infants are growth retarded.
- Perinatal mortality rate is 4–8 times higher for growth retarded fetuses.
- 10–25% of newborn in Pakistan are full term SGA.

Etiology

Maternal causes

- Chronic illness like essential hypertension, pregnancy induced hypertension, chronic renal disease, long-standing diabetes, and heart disease
- Young maternal age (<18 years)
- Poor maternal weight gain in pregnancy (<0.9 kg/every 4 weeks)
- Multiple pregnancy
- Poor socioeconomic status
- Malnutrition of mother

Fetal causes

- Chromosomal disorders (Trisomies 13,18, 21, Turner syndrome)
- Congenital infections (TORCH infection)
- Congenital malformation: renal dysgenesis/agenesis (Potter syndrome), congenital heart disease

Placental causes

- Decreased placental weight or cellularity or both
- Decrease in surface area
- Villous placentitis (viral, bacterial, parasitic)
- Infarction
- Placental sepration
- Tumor (chorioangioma, hydatidiform mole)
- Twin transfusion syndrome

Classification

Asymmetric growth retardation

- In these babies, weight of baby is more affected (<10th centile) than length or head circumference
- Mainly, placental insufficiency, maternal malnutrition, maternal age >35 years, multiple gestation lead to asymmetrical growth retardation

Symmetrical growth retardation

- In these babies, head size is also small in comparison to weight and length of the baby (all are <10th centile).
- Congenital infection, chromosomal disorders, and maternal drug use cause symmetrical growth retardation.

Term SGA

- When gestation is complete 37 weeks but weight is less for their gestation.

Preterm SGA

- Gestation is less and weight is also less to that gestation.

Problems of SGA

- **Hypoglycemia:** In 30% full term SGA, hypoglycemia is documented due to reduced glycogen deposits; heart and brain are large in proportion to rest of body. There is reduced catecholamine response, transient hyperinsulinemia, and hepatic gluconeogenesis is affected.
- **Hypothermia** due to large surface area to baby weight ratio, reduced subcutaneous fat.
- **Polycythemia** due to placental insufficiency (hypoxia), which leads to increased red cell mass. Polycythemia may also contribute to hypoglycemia and lead to cerebral injury.
- **Neutropenia** and **thrombocytopenia** due to hypoxia, temporary reduction in production of other cells like platelets and neutrophils except red blood cells.
- **Hypocalcemia:** exact cause is not known; but may be due to prenatal asphyxia.
- **Infections:** Increased risk of sepsis due to little reserves to fight against infections.
- **Congenital abnormalities:** 3–6% SGA have congenital abnormalities due to chromosomal disorders or by congenital infections, e.g. Potter syndrome, Cong. heart defects, limb defects, etc.
- **Perinatal asphyxia:** It is due to depleted liver and myocardial glycogen stores.
- **Meconium aspiration:** Due to increased chances of perinatal asphyxia, most SGA infants pass meconium during delivery and there is chance of aspiration during gasping.
- **Necrotizing enterocolitis** due to asphyxia.
- As adults more likely to have cardiovascular disease or hypertension.
- Type II diabetes mellitus.

Clinical findings

- A minority of infant will have congenital abnormalities, evidence of chromosomal abnormality and signs and symptoms of congenital infection.
- There is marked wasting particularly of thigh.
- The fingernails are mature and long and cracks and desquamation of skin begins after birth.
- The infant is usually active and vigorous with good sucking.

- The weight loss after birth is less marked in comparison to preterm.
- The accurate gestational age assessment shows signs of maturity.

Management

- Early obstetric diagnosis and planned delivery in the presence of Pediatrician is very important to do good resuscitation and for prevention of meconium aspiration and asphyxia.
- Infant should be carefully monitored for potential complications especially hypoglycemia and polycythemia; so glucose level should be checked frequently.
- Early feeding should be instituted. Start feeding milk at 1 hour of age, and then continue feeding every 2–3 hours. If oral feedings are not tolerated, feed by gavage (NG) or intravenously (TPN). SGA infants require more calories per kilogram for growth than AGA infants.
- Baby should be nursed in thermo-neutral environment.
- Evaluate and manage for congenital infections and congenital malformations. Chromosomal and genetic evaluation in suspected cases is indicated.

Prognosis/outcome

- Babies with asymmetrical growth retardation have potential for catch up growth within normal centile after birth if adequate calories are provided, while most of the infants with symmetrical growth retardation don't show catch up growth.
- By good perinatal care most of the babies have normal neurological outcome.
- IUGR infants with chromosomal disorders have 100% handicap rate, and with congenital infections have 50% handicap rate.

Difference between preterm and small for gestational age infants

- Both, preterm and SGA infants have increased incidence of hypoglycemia, hypocalcemia, infections, and feeding problems.
- Preterm infant has more chances to develop IRDS, apnea, and aspiration of feeds, jaundice, anemia, IVH, cerebral palsy, PDA, and kernicterus.
- SGA infant has more chances to develop meconium aspiration syndrome.

MECONIUM ASPIRATION SYNDROME

CASE

A ***post-term infant*** presents within half hour of birth. He was born at home after a ***prolongedand difficult labor***. He has ***fast breathing***. Infant has spit up some dark brown particulate fluid shortly after birth. On physical examination, he has marked respiratory distress. He has an umbilical cord and flaking skin with a ***yellow-green hue***. Chest radiograph reveals ***patchy infiltrates bilaterally***.

- Meconium is normally the first intestinal discharge of the newborn infant and is composed of epithelial cells, fetal hair, mucus, and bile.
- However, intrauterine stress may cause in utero passage of meconium into the amniotic fluid.
- Subsequent to passage, the meconium stained amniotic fluid may be aspirated by the fetus in utero or by the newborn during labour and delivery.
- If meconium is aspirated, it may cause intense inflammatory reaction, resulting in severe respiratory distress.
- The presence of meconium in amniotic fluid is a warning sign of fetal distress, calling for careful supervision of labour and assessment of fetal well-being.
- Meconium aspiration syndrome is a multi-organ disorder with perinatal asphyxia as the underlying cause.

Incidence

- Meconium-stained amniotic fluid is found in 10–15% of births.
- Meconium aspiration syndrome (MAS) develops in 5% of such infants.
- 30% require mechanical ventilation and 3–5% die.
- It most commonly occurs in post-term infants and infants who are small for gestational age (SGA) due to intrauterine growth retardation (IUGR). Both have placental insufficiency as a common pathway for fetal hypoxia.

Pathophysiology

- Asphyxia and other forms of intrauterine stress may cause increased intestinal peristalsis, with relaxation of internal anal sphincter and passage of meconium.
- The effect of intrauterine hypoxia on peristalsis and sphincter tone seems to increase with gestational age.
- After passage of meconium into the amniotic fluid, gasping respiration of the asphyxiated fetus, either in utero or during labor and delivery, can cause aspiration of the meconium stained amniotic fluid into the large airways of the lungs.
- The thick meconium causes total or partial airway obstruction, resulting in respiratory distress.
- In areas of total obstruction, atelectasis develops; but in areas of partial obstruction, a ball-valve phenomenon occurs, resulting in air trapping, hyperexpansion and air leaks.
- Ultimately, interstitial and chemical pneumonitis develops, with resulting bronchiolar edema and narrowing of the small airways.

- Uneven ventilation due to areas of partial obstruction and superimposed pneumonitis causes severe carbon dioxide retention and hypoxemia.
- Pulmonary vascular resistance increases as a direct result of hypoxia and acidosis, and hyperinflation of the lungs.
- The increase in pulmonary vascular resistance may lead to atrial or ductal right to left shunting and further desaturation.
- Infants with meconium aspiration syndrome are at increased risk of persistent pulmonary hypertension.

Risk factors

- Post-term pregnancy
- Preeclampsia-eclampsia
- Maternal hypertension
- Maternal diabetes mellitus
- Abnormal fetal heart rate
- Small for gestational age babies
- Biophysical profile <6
- Maternal heavy smoking, chronic respiratory disease, or cardiovascular disease

Clinical findings

- The presentation is quite variable.
- Symptoms depend on the severity of the hypoxic insult and the amount and viscosity of the meconium aspiration.
- Infants with meconium stained amniotic fluid often exhibit signs of post-maturity. They are small for gestational age with long nails and peeling skin stained with yellow or green pigment.
- These infants may have respiratory depression at birth, with poor respiratory effort and decreased muscle tone if there has been significant perinatal asphyxia associated with the passage of meconium.
- Heavily stained, thick 'pea soup like' meconium is associated with severe respiratory distress and higher morbidity and mortality rates than lightly stained, thin green meconium.
- If a large amount of thick meconium is aspirated, the infant presents with acute airway obstruction manifested by deep gasping respirations, cyanosis, and poor air exchange.
- The infant who has aspirated meconium into the distal airways but does not have total airway obstruction manifests signs of respiratory distress secondary to increased airway resistance and air trapping, i.e. tachypnea, nasal flaring, rib retraction, and cyanosis.
- Some infants who do not experience acute airway obstruction may have a delayed presentation, with only mild initial respiratory distress, which becomes more severe hours after delivery as chemical pneumonitis develops.
- There may be a noticeable increase in the anteroposterior diameter of the chest if air trapping develops.
- With air trapping, auscultation reveals decreased air exchange, i.e. variable rales, rhonchi, and wheezing.

Diagnosis

- Diagnosis is established by the presence of meconium in the tracheal or amniotic fluid combined with symptoms of respiratory distress.
- A chest X–ray film typically reveals hyperinflation of the lung fields and flattened diaphragms. Pneumothorax and pneumo-mediastinum may be present.
- Arterial blood gas levels characteristically reveal hypoxemia.

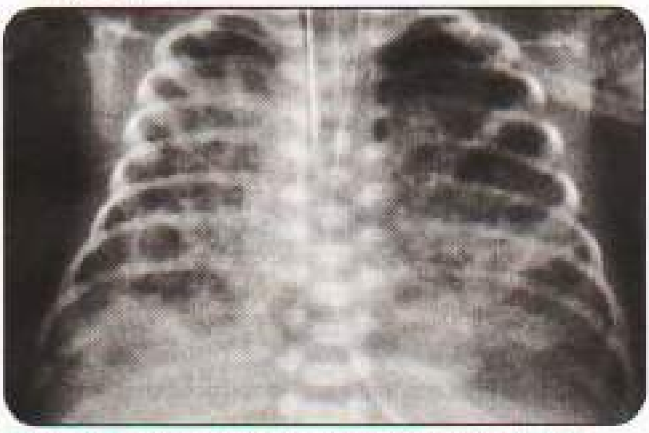


Figure 9.19: X-ray chest showing meconium aspiration.

Management

- Current management of a newborn delivered with meconium staining are following:
  - If the infant is vigorous with good respiratory effort and a heart rate >100 beats/minute, tracheal intubation to aspirate meconium should not be attempted. Mouth and nose may be suctioned with a bulb or suction catheter.
  - If the infant is depressed with poor muscle tone and/or a heart rate <100 beats/minute, first give breaths through ambu bag and if there isno chest rise with that then tracheal intubation and suctioning should be performed. The endotracheal tube should be attached to a suction device, and free-flow oxygen should be provided throughout the procedure.
  - Endogenous surfactant activity is inhibited by meconium.Exogenous surfactant therapy of MAS may improve oxygenation and reduce brochopulmonary complications.
- Persistent pulmonary hypertension (PPHN) also may coexist and should be vigorously treated (with oxygen, mechanical ventilation, inhaled nitric oxide, extracorporeal membrane oxygenation or occasionally with surfactant).

- Sildenafil (Viagra) is a selective phosphodiestrase type-I inhibitor, a potent vascular smooth muscle relaxant, particularly in lungs is usually used to treat PPHN. Dose is 1-3 mg/kg 6–12 hourly in neonates. For infants and children is 0.25–0.5 mg/kg/dose. Adverse effects are hypotension, increased risk of retinopathy of prematurity and platelet dysfunction.
- Meconium promotes the growth of bacteria. Since it is impossible to differentiate meconium aspiration from pneumonia radiographically, infants with infiltrates on chest X-ray film should be started on broad-spectrum antibiotics after appropriate cultures have been obtained.

Prognosis

- Complications are common and are associated with significant mortality.
- Ultimate prognosis depends on the extent of central nervous system injury from asphyxia.
- Treatment with high frequency ventilation, and inhaled NO (Nitrous Oxide) have reduced the mortality to <5%.

TRANSIENT TACHYPNEA OF THE NEWBORN

CASE

A term infant ***delivered via cesarean section*** develops ***tachypnea, grunting, flaring***, and ***retractions*** 10 minutes after birth. He has a respiratory rate of 70/minute. He has ***good tone, good color***, and a ***strong suck***. A chest radiograph reveals ***well-aerated lungs*** with ***fluid in the fissure*** on the right, ***prominent pulmonary vascular markings,*** and flat diaphragms. He has ***90% oxygen saturation***. He ***improves within few hours*** and requires no oxygen.

- Transient tachypnea is most common after cesarean delivery in full term newborn.

Definition

- It is a benign and self-limiting condition of newborn who have respiratory distress shortly after delivery that usually resolves within 3 days.

Incidence

- The incidence of transient tachypnea of newborn is 1–2% of all newborns.

Pathophysiology

- Delayed resorption of fetal lung fluid from the pulmonary lymphatic system.
- Increased fluid volume in lungs causes reduced lung compliance and increased airway resistance.
- This results in tachypnea and retractions.
- Elective cesarean section causes an increased risk because of lack of the normal vaginal thoracic squeeze, which forces lung fluid out.
- There is some evidence of pulmonary immaturity and mild surfactant deficiency.

Risk factors

- Elective cesarean section
- Male sex
- Excessive maternal sedation
- Macrosomia.

Clinical findings

- The infant shortly after birth has tachypnea (>60 breaths/minute).
- The infant may also have grunting, nasal flaring, subcostal and/or intercostal retractions, and occasional cyanosis that is relieved by minimal oxygen (<40%).
- These infants usually have good air entry without crepitations or rhonchi.
- No other signs of cardiac, CNS, hematologic, or metabolic disease and infections are present.
- Symptoms typically present for 12–24 hours in mild TTN, but may persist for 72 hours in severe TTN.

Investigations

- Arterial blood gases may show mild respiratory acidosis and mild hypoxemia.
- Complete blood cell count and differential may help to rule out infection.
- Chest X-ray shows hyperexpansion of the lungs, prominent pulmonary vascular markings, mild to moderate cardiomegaly, and flattening of the diaphragm. Fluid lines may be seen in the fissure, pleural space, or both.
- Hyperoxia test to rule out cyanotic congenital heart disease.

Differential diagnosis

- Idiopathic respiratory distress syndrome
- Pneumonia, sepsis
- Cyanotic congenital heart disease
- Birth asphyxia

Management

- It is usually supportive.
- Provide adequate oxygenation and in case of marked distress CPAP therapy is first and commonly used.
- Because of the risk of aspiration, an infant should not be fed by mouth if the respiratory rate is >60 breaths/minute. If the respiratory rate is <60 breaths/minute, oral feeding is given. If the rate is 60–80 breaths/minute, feeding should be given by nasogastric tube. If the respiratory rate is >80 breaths/minute, intravenous nutrition is indicated.

Prognosis

- TTN is a benign self-limited disease and usually lasts only 1–3 days with no risk of further pulmonary dysfunction.

HYPOGLYCEMIA

CASE

A full term baby girl is born at 37 weeks' gestation weighing 1800 g (*IUGR*). She is not taking feed and is pale and ***lethargic***. Her ***blood glucose*** is 30 mg/dL (***low***). Then she developed a ***seizure***.

Definition

- Hypoglycemia is defined as blood glucose level <40 mg/dl in a term or <30 mg in a preterm infant.
- **Transient hypoglycemia** is defined as hypoglycemia, which lasts for <7 days period.
- **Persistent hypoglycemia** which persists for >7 days period, and is mainly due to endocrine causes or insulin producing tumors.

Etiology

Decreased glucose stores/production

- Prematurity, postmaturity
- Small for gestational age or IUGR
- Inadequate feed or caloric intake

Increased utilization of glucose/hyperinsulinism

- Infant of Diabetic Mother (IDM)
- Erythroblastosis fetalis.
- Beckwith-Wiedmann syndrome
- Insulin producing tumors (nesidioblastosis)

Miscellaneous

- Sepsis
- Birth asphyxia
- Hypothermia
- Polycythemia
- After exchange transfusion
- Glycogen storage disease
- Hypopituitarism
- Maternal drugs (beta-blockers, e.g. propranolol).
- Galactosemia
- Large for gestational age infants

Incidence

- The overall incidence of symptomatic hypoglycemia in newborns varies between 1.3–3.0/1000 live births.
- Hypoglycemia occurs in 8.1% of full term LGA infants and 14.7% of SGA infants.
- 25–50% of infants of diabetic mothers and 15–25% of infants of mothers with gestational diabetes develop hypoglycemia.

General consideration

- Glucose crosses the placenta by facilitated diffusion, and fetal glucose levels are approximately 2/3rd of maternal levels.
- After the exogenous source of glucose is stopped by the cutting of the umbilical cord, newborn glucose levels rapidly fall to a low point in the first 1–2 hours of life.
- The levels then increase and stabilize at mean levels of 65–71 mg/dl by the age of 3–4 hours.
- Early feeding prevents hypoglycemia.
- Normal glucose requirement is 6 mg/kg/minute.

Clinical findings

- The onset of symptoms varies from a few hours to a week after birth.
- Hypoglycemia may be present without any symptom in high risk neonates; so high index of suspicion of hypoglycemia is required.
- In symptomatic babies, there may be:
    - Jitteriness or tremors
    - Apathy
    - Episodes of cyanosis
    - Convulsions
    - Intermittent apneic spells or tachycardia
    - Weak or high-pitched cry
    - Limpness or lethargy
    - Difficulty in feeding
    - Up rolling of eyes
    - Sweating
    - Sudden pallor
    - Hypothermia
    - Cardiac arrest and failure
- As these symptoms are non-specific and may be present in many neonatal diseases, disappearance of these symptoms after glucose infusion is suggestive for hypoglycemia.

Investigations

- **Blood glucose levels:** Initially may be measured by Dextrostix, but these reagent strips measure whole blood glucose, which is 15% lower than plasma levels. A confirmatory laboratory glucose determination is required before one can diagnose hypoglycemia. The glucose should be measured in high-risk infants at 1, 2, 4, 6, 12, and 24 hours of age; if the glucose level is stable, the monitoring can be discontinued if glucose level are above 50mg/dl prefeed in oralfeeding babies.
- **A complete blood count with differential** should be obtained to evaluate for sepsis.
- **Other investigations are needed in accordance with other diagnosis in suspicion.**

Complications

- CNS damage
- Intraventricular hemorrhage

Management

- Anticipation and prevention of hypoglycemia in infant at high risk of hypoglycemia is a very important step in management.

Blood glucose level 25–45 mg/dl: no symptoms of hypoglycemia

- Draw blood glucose for laboratory confirmation.
- If the infant is alert and vigorous, give feed and follow with frequent glucose monitoring.
- If the infant continues to have blood glucose <40–45 mg/dL or is unable to feed, provide intravenous glucose at 6 mg/kg/minute (D10W at 3.6 ml/kg/h).

Blood glucose level <45 mg/dl: symptoms of hypoglycemia present

- Draw blood glucose for laboratory confirmation.
- Provide bolus of D10W (2 ml/kg) followed by an infusion of 6 mg/kg/minute (3.6 ml/kg/h).

Blood glucose level <25 mg/dl: with or without symptoms of hypoglycemia

- Draw blood glucose for laboratory confirmation.
- Provide bolus of D10W followed by an infusion of 6 mg/kg/minute.
- If IV access cannot be obtained immediately, an umbilical vein line should be used.

Other measures for resistant or persistent hypoglycemia

- In resistant cases, maximum concentration of Dextrose may be given (12.5% in peripheral vein or 25% in central vein).
- Treatment is gradually reduced and then discontinued when serum glucose remains above 45 mg/dl and the infant is asymptomatic for 24–48 hours and is taking adequate oral feeding.
- In case of persistent hypoglycemia, other medicines along with glucose infusion are given:
  - Octreotide dose 5-20ug/kg/day subcutaneously or intravenously divided every 6-8 hours.
  - Diazoxide (in case of hyperinsulinemia) 5-8 mg/kg/day PO in 2–3 divided doses.
- Surgery is considered in case of insulin producing tumors.

Prognosis

- The prognosis of hypoglycemia is good if therapy is prompt.
- CNS sequelae are seen in infants with neonatal seizures resulting from hypoglycemia and in neonates with persistent hyperinsulinemic hypoglycemia.

HYPOCALCEMIA

CASE

A 2-day-old infant presents with ***convulsions***. His mother has diabetes mellitus and pregnancy-induced hypertension. In clinical investigations, serum bicarbonate level is 22 meq/dL, ***serum calcium is 6.2 mg/dL*** and serum glucose is 70 mg/dL.

Definition

- Hypocalcemia is defined as total calcium level <7 mg/dl OR ionized calcium level of <3 mg/dl.
- **Early onset hypocalcemia** occurs during the first 3 days of life.
- **Late onset hypocalcemia** occurs after the 3 days of age.

Incidence

- About 50% of low birth weight and nearly all very low birth weight infants have hypocalcemia.
- 25–50% of infants of diabetic mothers have hypocalcemia during first 24–48 hours.

Etiology/risk factors

Early onset hypocalcemia

- Preterm infants (target organ responsiveness to PTH may be diminished)
- Infants of diabetic mothers (due to increased Calcium demand, hypercalcitoninemia, hypoparathyroidism, abnormal Vitamin D metabolism)
- Birth asphyxia (related to renal insufficiency, acidosis, and impaired PTH secretion or responsiveness)
- Infants with poor enteral intake
- Infants stressed during the perinatal period
- Infants receiving citrated blood transfusions; Exchange transfusion
- Infants receiving diuretics
- Meconium aspiration, respiratory distress syndrome
- Bicarbonate therapy; alkalosis

Late onset hypocalcemia

- Hyperphosphatemia (excessive intake of cow's milk; renal disease)
- Shock, sepsis
- Magnesium deficiency (Mg <1.5 mg/dl)
- Idiopathic, transient hypopara-thyroidism
- Congenital hypoparathyroidism (DiGeorge's sequence)
- Maternal hyperparathyroidism
- Vitamin D deficiency secondary to maternal vitamin D deficiency and maternal anticonvulsant therapy.
- Alkalosis, bicarbonate, and citrated blood transfusions

Clinical findings

- Hypocalcemia increases cellular permeability to sodium ions and increases cell membrane excitability.
- The signs are usually non-specific i.e. apnea, seizures, jitteriness, poor feeding, lethargy, increased extensor tone, clonus, hyperreflexia, stridor (laryngospasm), cardiac arrhythmias, and tetany (rare).
- Early onset hypocalcemia in preterm newborns is usually asymptomatic or clinically mild but late onset hypocalcemia usually presents as hypocalcemic seizures.

Investigations

- **Serum calcium levels:** Suggested schedule for monitoring calcium level in infants at risk of developing hypocalcemia is:
    - Preterm infants >1000 g: At 24 and 48 hours of age.
    - Preterm infants <1000 g: At 12, 24, and 48 hours of life.
    - Sick or stressed infants: At 12, 24, 48 hours and then as indicated.
    - Healthy preterm infants >1500 g and healthy IDMs need not be monitored in the absence of symptoms.
- Serum phosphate, magnesium, alkaline phosphate levels when indicated.
- ECG: Prolonged corrected Q–T interval longer than 0.4 seconds (due to prolonged systole).

Management

- Anticipation and prevention of hypocalcemia is much important.
- In asymptomatic, healthy preterm infants no treatment is required except normal maintenance calcium in their IV fluids.
- Symptomatic hypocalcemic infants should receive a slow IV bolus of 1–2 ml/kg of 10% calcium gluconate, given diluted in 5% Dextrose, over 5 minutes. Monitor heart rate for bradycardia and infusion site for extravasation. Repeat the dose in 10 minutes if there is no clinical response.
- Following the initial dose, maintenance calcium should be given parenterally or orally. IV dose is 200–500 mg/kg/day (2–5 ml/kg/day) of 10% calcium gluconate in divided doses in infusion. Oral dose is 40–75 mg/kg/day of elemental calcium in divided doses.
- Symptomatic hypocalcemia unresponsive to calcium therapy may be due to hypomagnesemia. IM dose is 0.1–0.2 ml/kg of 50% $MgSO_4$. Oral dose is 100 mg (0.2 ml)/kg/day of 50% $MgSO_4$.
- Treat the specific and chronic causes of hypocalcemia:
    - Reduce renal phosphate load by discontinuing cow's milk feeding and feeding the infant breast milk, or increase the $Ca:PO_4$ ratio of cow's milk to 4:1 with oral calcium supplements. This will inhibit intestinal phosphorus absorption.
    - Hypoparathyroid infants are given low phosphate, high calcium diet, and Vit D $_3$ in Vitamin D deficiency if present.
    - In case of Vitamin D deficiency, Vitamin D is given (oral Vitamin D_2 5000 units per day).

Prognosis

- Hypocalcemia can be effectively controlled with close monitoring of calcium, phosphate, and vitamin D intake and urinary calcium losses.

INFANT OF DIABETIC MOTHER (IDM)

CASE

A newborn presents with ***jitteriness***. His ***weight*** is ***4 kg***. Physical examination shows a large, plethoric infant who is tremulous. A murmur is heard. ***Blood sugar*** is ***low*** (35 mg/dl). Mother had gestational diabetes during pregnancy.

Definition

- This is a condition or a set of complications in the baby when adequate control of diabetes mellitus has not been accomplished in the mother during pregnancy.

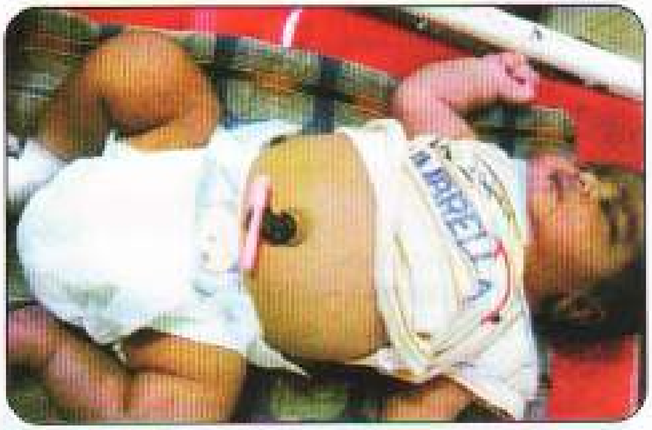


Figure 9.20: Infant of diabetic mother

Incidence

- Insulin-dependent diabetes occurs in 0.5% of all pregnancies.
- In addition, 1–3% of women exhibit biochemical abnormalities during pregnancy consistent with gestational diabetes.

Pathophysiology

- Maternal hyperglycemia causes fetal hyperglycemia, and the fetal pancreatic response leads to fetal hyperinsulinemia.
- Fetal hyperinsulinemia and hyperglycemia then cause increased hepatic glucose uptake and glycogen synthesis, accelerated lipogenesis, and augmented protein synthesis.
- The separation of the placenta at birth suddenly interrupts glucose infusion into the neonate without a proportional effect on the hyperinsulinism, resulting in hypoglycemia and attenuated lipolysis during the first hours after birth.
- Congenital anomalies correlate with poor metabolic control and may be due to hyperglycemia-induced teratogenesis.

Clinical findings

- Large and plump baby (macrosomia) as a result of increased body fat and enlarged viscera, with puffy, plethoric facies.

- Infants may, however, also be of normal or low birth weight, particularly if they are delivered before term or if there is associated maternal vascular disease.
- Infants may be jumpy, tremulous, and hyperexcitable during the first 3 days of life, although hypotonia, lethargy, and poor sucking also may occur. Early appearance of these signs is more likely to be related to hypoglycemia and later appearance related to hypocalcemia. These abnormalities also may occur together.
- Signs of respiratory distress secondary to immature lungs can be noted on examination.
- Cardiac disease may be present as an enlarged cardiac shadow on chest X-ray film or by physical evidence of heart failure.
- Gross congenital anomalies may be noted on physical examination.

Table 9.13: Observation of the IDM in the Resuscitation Room.

Asphyxia
Birth injury
Congenital malformations
Evidence of macrosomia
Hypoglycemia
Respiratory distress

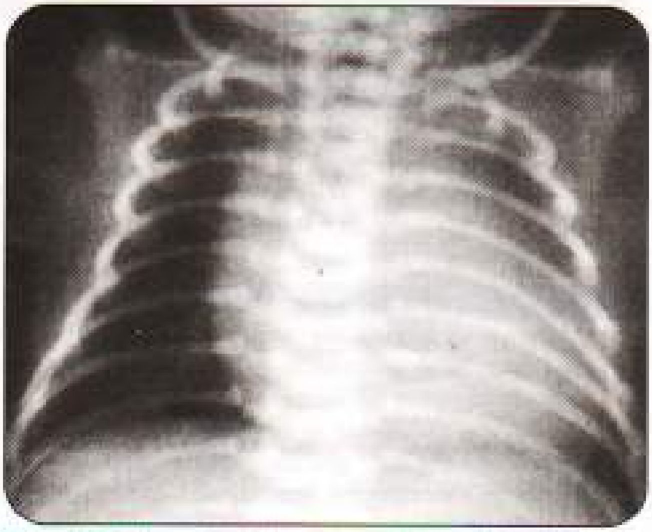


Figure 9.21: X-ray chest showing cardiomegaly in IDM.

Complications

- Macrosomia
- Organomegaly
- Small for gestational age
- Hypoglycemia
    - It is present in up to 40% of IDMs, most commonly in macrosomic infants.
    - It usually presents within 1–2 h after delivery.
- Hypocalcemia
    - The incidence is up to 50% of IDMs. The severity of hypocalcemia is related to the severity of maternal diabetes and involves decreased function of the parathyroid glands. Serum calcium levels are lowest at 24–72 h of age.
- Hypomagnesemia
- Birth asphyxia (25%)
    - May result from prematurity, cesarean delivery, intrauterine hypoxia caused by maternal vascular disease, or macrosomia
- Birth trauma (Klumpke or Erb paralysis, shoulder dystocia, clavicle fracture, cephalhematoma, etc).
- Respiratory distress syndrome (3%)
    - Mostly due to premature delivery, delayed maturation of pulmonary surfactant production, or delivery by elective cesarean section. Fetal hyperinsulinism may adversely affect the lung maturation process in the IDM by antagonizing the action of cortisol.
- Transient tachypnea of newborn
- Hypertrophic cardiomyopathy (50%)
    - It occurs secondary to increased fat and glycogen deposition in the myocardium and may lead to congestive cardiac failure.
- Hyperbilirubinemia
- Polycythemia and hyperviscosity
- Renal venous thrombosis
- Congenital malformations (6.4%)
    - Cardiac (transposition of the great vessels, ventricular septal defects, or atrial septal defects)
    - Renal defects (e.g. agenesis)
    - GIT defects (e.g. small left colon syndrome or situs inversus)
    - Neurologic defects (e.g. neural tube defects or holoproencephaly)

Investigations

- Serum glucose levels should be checked at delivery and at ½, 1, 1 ½, 2, 4, 8, 12, 24, 36, and 48 hours of age or the monitoring can be discontinued if glucose level are above 50mg/dl prefeed in oralfeeding babies.
- Serum calcium levels should be obtained at 6, 24, 48 hours of age.
- The hematocrit should be checked at birth and at 4 and 24 hours of age.
- Serum bilirubin levels should be checked as indicated by physical examination.
- Arterial blood gases, CBC, cultures, and gram stains should be obtained as clinically indicated.
- Radiological studies are not necessary unless there is evidence of cardiac, respiratory, or skeletal problems.
- ECG and echocardiography should be performed if hypertrophic cardiomyopathy or a cardiac malformation is suspected.

Table 9.14: Causes of Respiratory Distress in the IDM.

Respiratory distress syndrome
Cardiac disease
Meconium aspiration
Pneumothorax
Transient tachypnea

Management

- Upon delivery, regardless of size, infants of diabetic mothers should initially receive close observation and care.
- In the nursery, blood glucose levels and the hematocrit should be obtained.
- Start feeding when baby is stable and is able to suck, and has no apparent complications (preferably within 1 hour after birth). Feeding is the initial treatment for hypoglycemia. Encourage breastfeeding.
- The infant should be observed for jitteriness, tremors, convulsions, apnea, weak cry, and poor sucking.
- A physical examination should be performed, paying particular attention to the heart, kidneys, lungs, and extremities.
- The target plasma glucose concentration is ≥45 mg/dL before feeds.
- Treatment of hypoglycemia is indicated if the plasma glucose is <45 mg/dL and clinical symptoms of hypoglycemia are present.
- In asymptomatic infants, treatment is indicated if the plasma glucose is <30 mg/dL.
- For hypoglycemia, infuse a bolus of 2 ml/kg of 10% glucose solution at a rate of 1.0 ml/minute. Then give a continuous infusion of 10% glucose at a GIR i.e glucose infusion rate of 6–8 mg/kg/minute,(equal to 85ml/kg/day to 115ml/kg/day 10% dextrose water respectively) and increase the rate as needed to maintain normal blood glucose (>45–50 mg/dl). The level should be followed every 30–60 minutes until stable.
- The highest concentration of glucose that can be infused through a peripheral line is 12.5%.
- If an intravenous line cannot be started, glucagon can be given to infants with adequate glycogen stores.
- Other complications e.g. hypocalcemia, hypomagnesemia, RDS, birth asphyxia, cardiomyopathy, hyperbilirubinemia, polycythemia, etc. should be managed accordingly.

Prognosis

- The morbidity and mortality is decreased with adequate control of diabetes during the diabetic pregnancy.
- The risk of subsequent diabetes in the infants of these women is at least 10 times greater than in the normal population.
- Physical development is normal, but childhood obesity is common in infants of diabetic mothers.

NEONATALSEIZURES

CASE

A full term newborn presents at the age of 2 hours with jerking blinking of eyes (*fits*) and apneic spells. He is delivered by ***obstructedlabor***. There is history of ***delayed cry***. On examination, he is pale with bradycardia and ***bulging fontenella***.

Definition

- A seizure is defined clinically as a paroxysmal alteration in neurologic function (i.e. behavioral, motor, or autonomic function, or all three).
- Seizures may be ***early onset*** (0–3 days of age) or ***late onset*** (after 3 days of age).

Incidence

- Neonatal seizures are not uncommon.
- The incidence ranges from 1.5–14 in 1000 live births.
- In 60% of cases hypoxic ischemic encephalopathy, in 15% of cases intracranial hemorrhage, and in 12% of cases infection is the cause of seizures.
- In 10% of cases no cause is found.

Pathophysiology

- Depolarization occurs as a result of inward influx of sodium in neurons within the CNS. Repolarization occurs via efflux of potassium.
- A seizure occurs when there is excessive depolarization, resulting in excessive synchronous electrical discharge.
- The basic mechanisms of neonatal seizures are unknown, however, four possible reasons for excessive depolarization are described below:
- Failure of the sodium-potassium pump because of a disturbance in energy production.
- A relative excess of excitatory activity in the hippocampus and neocortical region of brain.
- The proconvulsant network of substantia niagrra is fully functional while anticonvulsant network develops later.
- Alterations in the neuronal membrane, causing inhibition of sodium movement.
- There is delayed maturation of postsynaptic inhibitory system.

Clinical types of seizures in neonates

- Due to incomplete glial proliferation, neuronal migration, establishment of axonal and dendritic contacts, and myelin deposition in the neonatal brain, seizures in the neonates are different from those seen in older children.
- There are no tonic-clonic seizures in neonates.
- Neonatal seizures have adverse effect on the developing brain. There is rich network of excitatory glutamate receptors and failure of energy reserve

replenishment results in neuronal cell injury or death. Aberrant neurogenesis and sprouting of fibers increase the risk of further seizures and cognitive loss.

Subtle seizures

- Constitute 50% of seizures in neonates and are more common in preterm than in full-term infants.
- They consist of tonic horizontal deviation of the eyes with or without jerking; eyelid blinking or fluttering, sucking, smacking, or drooling, swimming rowing or pedaling movements, and apneic spells.

Clonic seizures

- These are more common in full-term than in preterm infants.
- **Focal clonic seizures:** The movements involve well-localized clonic jerking.

Tonic seizures

- These occur primarily in premature infants.
- **Focal tonic seizures:** Sustained posturing of a limb, asymmetric posturing of the trunk or neck, or both.

Myoclonic seizures

- These are seen in both full-term and preterm infants and are characterized by single or multiple synchronous jerks.
- **Focal myoclonic seizures** involve the flexor muscles of an upper extremity.
- **Multifocal myoclonic seizures** involve asynchronous twisting of several parts of the body.
- Perinatal asphyxia, hypoxic ischemic encephalopathy
- Intracranial hemorrhage
- Metabolic abnormalities
  - Hypoglycemia
  - Hyponatremia
  - hypernatremia
  - Hypocalcemia
  - Hypomagnesemia
- Infections (meningitis, sepsis, TORCH)
- In born errors of metabolism (e.g. phenyleketoneuria, galactosemia)
- Congenital malformations
- Kernicterus
- Tetanus neonatorum
- Pyridoxine dependency
- Drug withdrawal (narcotics, benzo-diazepines, barbiturates)
- Familial neonatal seizures

Evaluation

- Age of the neonate is important. Birth asphyxia and birth trauma cause convulsions during the first day of life but uncommonly after 3 days of age. Hypoglycemia also presents during the same period in a sick or high risk infant. Early hypocalcemic seizures in premature or sick infant occur in the first 3 days of life, while late hypocalcemic seizures occur in healthy full-term infant at 5–7 days of age. Seizures due to infections or congenital malformations of brain may present at any time. Tetanus neonatorum presents after 4 days of life. Pyridoxine dependency causes seizures shortly after birth. The onset of drug withdrawal and hyponatremic or hypernatremic seizures may occur at any time during neonatal period.
- Seizures caused by birth asphyxia or birth trauma are preceded by lethargy for several hours, followed by seizures at the end of first day of life. Convulsions due to hypoglycemia or early hypocalcemia occur in ill infants while infants with late hypocalcemia are generally vigorous, alert and appear healthy between seizures. In meningitis, there may be fever or bulging fontanel.
- Family history of seizures may be present in case of inborn errors of metabolism and benign familial neonatal convulsions.
- Maternal drug history and details of delivery are also important.

Investigations

These usually depend on the information obtained by history and physical examination.

- Blood glucose, calcium, electrolytes, magnesium, phosphate, urea, and creatinine
- Complete blood count, culture and septic screen
- CSF examination to exclude meningitis or sepsis
- Metabolic profile in case of inborn errors of metabolism
- Cranial USG or CT scan to rule out intracranial hemorrhage, brain malformations, calcifications (in case of CMV or toxoplasmosis)
- EEG.

Management

General measures

- Ensure clear airway and support ventilation by giving oxygen inhalation.
- Set up an IV line for infusions.
- Maintain baby's temperature.
- Put nasogastric tube and aspirate stomach contents to prevent vomiting and choking.
- Keep NPO (nothing per oral) until seizures are controlled.
- Monitor heart rate, respiratory rate and skin perfusion.
- Send sample to laboratory for blood chemistries.

Specific measures

- Give 10% Dextrose water 2–4 ml/kg IV to control hypoglycemia. If seizures are controlled, give continuous infusion 6–8 mg/kg/minute.
- If seizures are not controlled in a few minutes, give 10% calcium gluconate 2 ml/kg IV slow diluted in 5 minutes under cardiac monitoring. If seizures are

controlled, give maintenance calcium IV or oral. Hypomagnesemia may also be corrected.

- If seizures are still not controlled then anticonvulsant therapy is started.
- Phenobarbitone is the drug of first choice. 20 mg/kg loading dose is given IV diluted over 10–20 min. If seizures are controlled, maintenance dose 5 mg/kg/day is given orally. It may be combined with phenytoin and its efficacy is increased up to 63%. Phenytoin is given. 10–20 mg/kg as loading dose followed by maintenance dose of 4–8 mg/kg/day IV or oral in divided doses.
- If seizures are not controlled, other anticonvulsants may be tried. Diazepam, initial dose 0.1–0.3 mg/kg IV slow diluted is given and may be repeated after 10 minutes. Continuous infusion may be given or phenobarbitone may be started as maintenance anticonvulsant.
- In intractable seizures pyridoxine may be given. Dose is 50–100 mg/kg IV.
- Newer drugs:
    - Levertiracetaminmay be given in a dose of 10-30mg/kg/day. It is new drug commoly used having few side effects.
    - Felbamate, levetiracetam and lamotrigine may also be used. Lamotrigine needs slow titration as it may cause life threatening allergic rash.

Duration of anticonvulsant therapy

- Optimal duration has not been established.
- In uncomplicated cases, it may be stopped at the time of discharge when seizures have been controlled.
- In complicated cases, it may be stopped after seizures have been absent for 2 weeks.
- In recurrent seizures, prolonged therapy may be needed.

Prognosis

- The prognosis varies with the cause. Infants with hypocalcemic seizures have an excellent prognosis, while those with seizures due to congenital malformations have a poor prognosis.
- Risk of later epilepsy is 10-30%.

HEMORRHAGIC DISEASE OF THE NEWBORN INFANT (VITAMIN K DEFICIENCY)

CASE

A 4-day-old infant ***born at home*** (so vitamin K not given) presents with ***bloody stools*** and ***purpura***. Blood is oozing from his circumcision site. The pregnancy was without complications. He was healthy since birth.

Definition

- It is a temporary coagulation defect due to vitamin K deficiency resulting in spontaneous hemorrhage.

Incidence

- Hemorrhagic disease of the newborn occurs in 0.25–1.7% of neonates not given vitamin K prophylaxis.

Pathophysiology

- Hemorrhagic disease of newborn is due to deficiency of vitamin K dependent factors (factors II, VII, IX, and X).
- Most babies have moderate deficiency of these factors by 48–72 hours after birth, with gradual return to normal levels by 7–10 days of age.
- This transient deficiency of vitamin K dependent factors is due to lack of the free vitamin K in the mother and thus in the baby, immaturity of the newborn's liver, and absence of bacterial intestinal flora normally responsible for synthesis of vitamin K.
- Breast milk is a poor source of vitamin K, so breast-fed infants are more prone to hemorrhagic disease that usually occurs between 3–5 days of life.

Etiology

Early onset: (0–24 hours of age)

- Maternal drugs (phenobarbitone, phenytoin, warfarin, rifampicin, isoniazid) that interfere with vitamin K
- Inherited coagulopathy

Classic disease: (2–7 days of age)

- Breastfeeding
- No vitamin K prophylaxis at birth

Late onset: (1–6 months)

- Cholestasis–malabsorption of vitamin K (biliary atresia, cystic fibrosis, hepatitis).
- Chronic diarrhea, malabsorption syndrome.
- Prolonged antibiotic therapy (suppression of colonic bacteria).

Clinical findings

- Baby may present with bleeding from the gut, hematemesis, vaginal bleeding, or hematuria.
- Bleeding may occur from umbilical cord, circumcision site, injection site, scalp (cephalhematoma), mucosa, and skin.
- Intracranial hemorrhage may occur as a fatal complication.

Investigations

- Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), and clotting time (CT) are prolonged.
- Levels of factor II (prothrombin), VII, IX, and X are significantly reduced.
- Bleeding Time (BT), fibrinogen, factor V and platelets are normal.
- The diagnosis is confirmed by a demonstration of noncarboxylated protein in vitamin K absence (PIVKA) in the plasma and by improvement following treatment with vitamin K.

Prevention

- Vitamin K should be given to all newborns prophylactically at birth. Dose is 1 mg IM.
- Intramuscular route is the method of choice, but if vitamin K is given orally it is given 1–2 mg at birth, then at the time of discharge, and then after 3–4 weeks (total 3 doses).

Management

- Treatment with vitamin K should be given immediately and not withheld awaiting test results.
- Injection vitamin K is given 1–5 mg IV, with improvement of coagulation defects and cessation of bleeding within a few hours. IM injections should be avoided in infants who are bleeding.
- Serious bleeding, particularly in premature infants or those with liver disease, may require a transfusion of fresh frozen plasma (10 ml/kg) or whole blood (20 ml/kg).

Differential diagnosis

- **Swallowed blood syndrome:** It presents as bloody stool passed on 2nd or 3rd day of life. Maternal blood ingestion is the most common cause of suspected GI bleeding. Blood can be swallowed during delivery or while an infant is breastfeeding (from a fissure in the mother's breast). It is diagnosed by Apt test which differentiates maternal blood from fetal blood.
- **The Apt test** is used to rule out maternal blood. If the child is well and only GI bleeding is noted, an Apt test is performed on gastric aspirate or stool to rule out the presence of maternal blood swallowed during labor or delivery or from a bleeding breast. A breast pump can be used to collect milk to confirm the presence of blood in the milk, or the infant's stomach can be aspirated before

  and after breastfeeding.
  a. **Procedure.** Mix one part bloody stool or vomitus with five parts water; centrifuge it and separate the clear pink supernatant (hemolysate); add 1 mL of sodium hydroxide 1% (0.25 M) to 4 mL of hemolysate.
  b. **Result.** Hemoglobin A (HbA) changes from pink to yellow brown (maternal blood); hemoglobin F (HbF) stays pink (fetal blood).
- **Withdrawal bleeding:** Mild bleeding may occur in a healthy girl on the 3rd day. It is due to maternal estrogen withdrawal effect.
- **Disseminated intravascular coagulation (DIC):** It usually occurs in sick newborns. There is widespread bleeding from different sites. There is thrombocytopenia, decreased plasma fibrinogen level, and raised Fibrin Degradation Products (FDP). It is treated by correcting primary clinical problem, e.g. infection, and whole blood or plasma as replacement therapy.
- **Hemophilia:** Bleeding is not controlled with vitamin K. Factor VIII (hemophilia A) or factor IX (hemophilia B) is deficient. Treatment is fresh whole blood or specific factor replacement.
- **Isoimmune neonatal thrombocytopenia:** Neonate presents with petechial hemorrhage or bleeding from the bowel or hematuria. There is thrombocytopenia due to maternal antibody destruction.. Corticosteroid and IVIG therapy are other treatment options.
- **Peptic ulcer:** Rarely, it presents as hemetemesis or melena in neonatal period. Large hemorrhage may lead to sudden collapse.

Prognosis

- Hemorrhagic disease of the newborn has not been reported in infants who received IM vitamin K at birth.
- If there is no intracranial hemorrhage, prompt and early treatment carries a good prognosis.

ANEMIA IN NEWBORN INFANT

CASE

A ***full term*** 2.5 kg baby boy was born at home. On presentation, he appears ***pale***. Physical examination is otherwise normal. Maternal blood group is A positive. Baby blood group is O positive (***no blood group incompatibility***). ***Hematocrit*** is ***38%*** and reticulocyte count is 5%.

Definition

- It is defined as hemoglobin or hematocrit concentration of greater than 2 SD (standard deviation) below the mean for that age.

Etiology

- There are three main causes of anemia in neonates:

Blood loss

- Obstetric causes of blood loss:
  - Abruptio placentae
  - Placenta previa
  - Incision of placenta at cesarean section
  - Rupture of cord.
- Occult blood loss:
  - Fetomaternal bleeding
  - Fetoplacental bleeding
  - Twin-to-twin transfusion
  - Bleeding in the neonatal period:
  - Intracranial bleeding
  - Massive cephalhematoma
  - Bleeding from umbilicus
  - Adrenal or renal hemorrhage
  - Gastrointestinal bleeding
- Iatrogenic causes: Blood sampling with inadequate replacement.

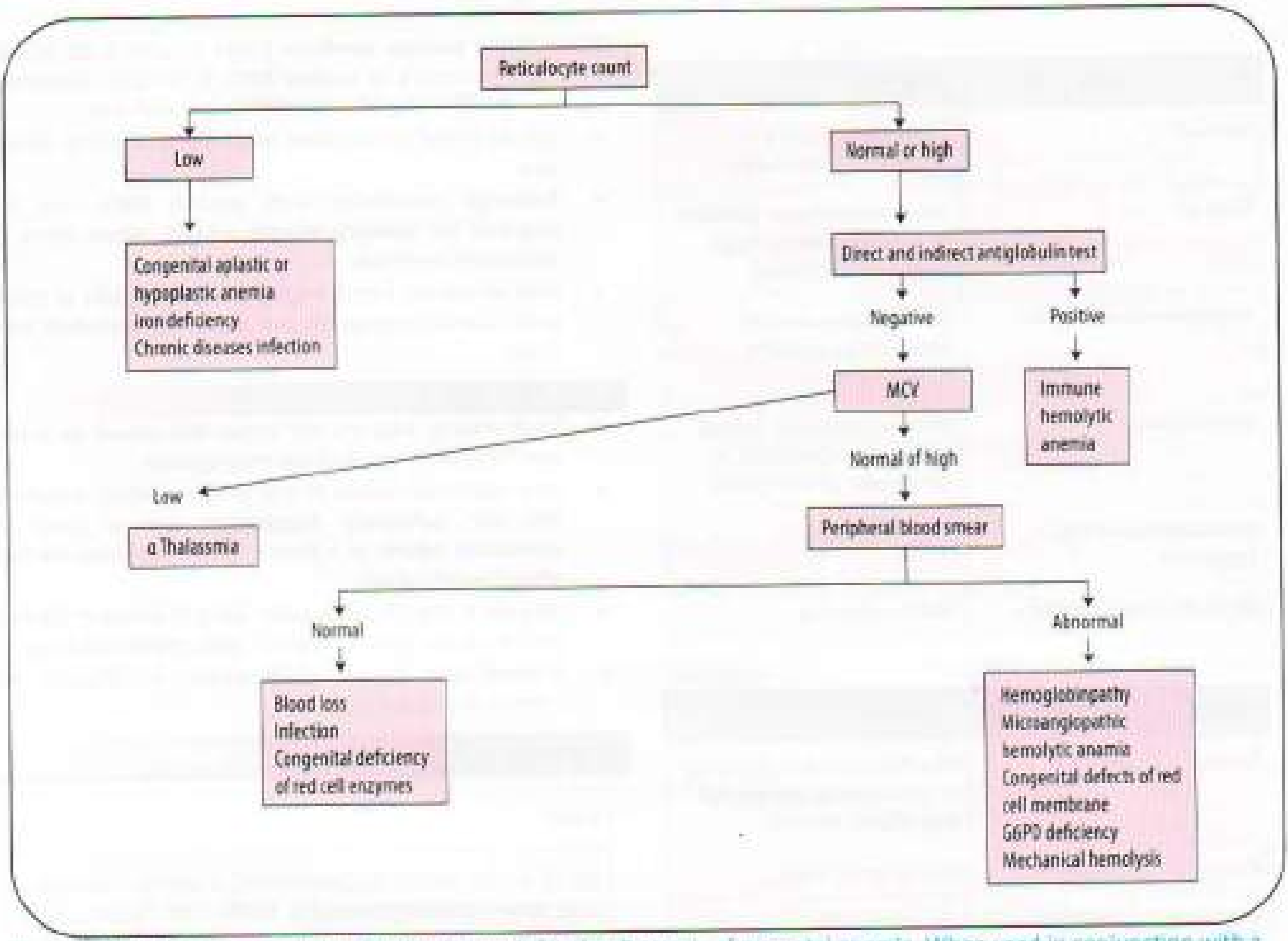

Reticulocyte count
Low
Normal or high
Congenital aplastic or hypoplastic anemia
Iron deficiency
Chronic diseases infection
Direct and indirect antiglobulin test
Negative
Positive
MCV
Immune hemolytic anemia
Normal of high
Low
α Thalassmia
Peripheral blood smear
Normal
Abnormal
Blood loss
Infection
Congenital deficiency of red cell enzymes
Hemoglobinpathy
Microangiopathic hemolytic anamia
Congenital defects of red cell membrane
G6PD deficiency
Mechanical hemolysis

Figure 9.22: Laboratory algorithm for the diagnosis for the diagnosis of neonatal anemia. When used in conjunction with a complete history and physical examination, the cause of the anemia often can be identified.

Hemolysis

- Immune hemolysis:
  - Rh incompatibility
  - ABO incompatibility
  - Minor blood group incompatibility
  - Maternal SLE
- Hereditary RBC disorders:
  - Spherocytosis
  - G6PD deficiency
  - Alpha thalassemia
- Acquired hemolysis:
  - Sepsis
  - DIC
  - Vitamin E deficiency

Diminished RBC production

- Diamond-Blackfan syndrome
- Osteopetrosis
- Anemia of prematurity
- Fanconi's anemia
- Congenital leukemia

Diagnostic approach to anemia

- The family history should include questions about:
  - Anemia (Fanconi's anemia)
  - Jaundice
  - Gallstones
  - Splenectomy
- The obstetric history should be evaluated for antenatal hemorrhage.
- The physical examination may provide a clue to the origin of the anemia:
  - Acute blood loss (shock, cyanosis, poor perfusion, acidosis)
  - Chronic blood loss (pallor, mild symptoms of respiratory distress or irritability)
  - Chronic hemolysis (pallor, jaundice, hepatosplenomegaly)
- Complete blood cell count.
- Reticulocyte count:
  - Elevated with chronic blood loss and hemolysis
  - Depressed with infection and production defect
- Blood smear:
- Coombs' test and bilirubin level
- Apt test

Table 9.15: RBC morphology and its diagnosis.

RBC morphology	Diagnosis
Normal	Physiologic anemia of infancy or prematurity
Normal	Acute hemorrhage infection or enclosed hemorrhage (cephalohematoma).
Hypochromic microcytic	Chronic fetomaternal hemorrhage or alpha thalassemia.
Spherocytes	Immune hemolysis (blood group incompatibility) or hereditary spherocytosis.
Schistocytes and RBC fragments	DIC
Bite cells (Heinz bodies)	G6PD deficiency.

Table 9.16: Bilirubin level, coombs' test and their diagnosis.

Bilirubin	Coombs' test	Diagnosis
Normal	Normal	Physilogic anemia of infancy or prematurity, congenital hypoplastic anemia.
Normal	Negative	Acute hemorrhage
Increased	Negative	Hereditary spherocytosis, G6PD deficiency.
Increased	Positive	Immune hemolysis (blood group incompatibility)

- Kleihaur test of the mother's blood
- Ultrasound of abdomen and head
- Tests on parents (CBC, smear, RBC indices, RBC enzymes e.g. G6PD deficiency, and blood group
- Studies for infection (TORCH infection), bacterial cultures and viral titres

Management

Blood transfusion

- Indications:
    - Infants with significant respiratory disease or congenital heart disease, with hematocrit <35–40%.
    - Infants with ABO incompatibility who do not have an exchange transfusion.
    - Premature babies with sepsis, pneumonia, etc.
- Packed RBCs: The volume of transfusion may be calculated as follows:

  Weight in kg × blood volume per kg × (hematocrit desired–hematocrit observed)/hematocrit of blood to be given
    - The average newborn blood volume is 80 ml/kg. Hematocrit of packed RBCs is 60–90%. Generally 15–20 ml/kg of packed RBCs is transfused.
- Whole blood is indicated when there is acute blood loss.
- Exchange transfusion with packed RBCs may be required for severely anemic infants, when there is circulatory overload.
- Give elemental iron 6 mg/kg/day for 6 weeks to treat anemia and continue for 3–4 months to replenish iron stores.

Prophylaxis

- Term infants, who are not breast fed, should be given iron-fortified formula (2 mg iron/kg/day).
- Iron supplementation in the preterm infant prevents late iron deficiency. Supplement iron is given in premature infants at a dose of 2–4 mg/kg/day started after 2 weeks of age.
- Vitamin E (15–25 IU) is given daily in preterm infants until the baby is 38–40 weeks' post-conceptional age.
- Recombinant human erythropoitin is effective in anemia of prematurity.

POLYCYTHEMIA IN NEWBORN INFANT

CASE

At 38 weeks' gestation (***post-term***), a woman delivers a 2 kg infant (***low-birth-weight, IUGR***) with Apgar scores of 1 at 1 minute and at 5 at 5 minutes. He has tachypnea. Laboratory studies at 18 hours of age show a hematocrit of 79% (***polycythemia***), platelet count of 100,000/µL (thrombocytopenia), glucose 38 mg/dL, magnesium 2.5 meq/L, and calcium 8.7 mg/dL. Now, he has a generalized seizure.

Definition

- Polycythemia is defined as a venous hematocrit of over 65%.
- When the hematocrit increases to more than 60%, there is a fall in oxygen transport.
- Newborns have erythrocytes that are less deformable than the erythrocytes of adults.

Increase in blood viscosity (friction to flow)
↓
Impairment of tissue oxygenation
↓
Decreased glucose in plasma
↓
A tendency to form micro-thrombi
↓
Significant damage may occur in cerebral cortex, kidneys, or adrenal glands
↓
Hypoxia and acidosis increase viscosity and deformity further
↓
Poor perfusion increases the possibility of thrombosis

Incidence

- The incidence of polycythemia in newborn is increased in babies who are small for gestational age and in post-term babies.

Causes of polycythemia

- Delayed cord clamping (more than 1 minute after birth)
- Cord stripping (thus pushing more blood into the infant)
- Holding the baby below the mother at delivery
- Maternal-to-fetal transfusion
- Twin-to-twin transfusion
- Forceful uterine contractions before cord clamping
- Placental insufficiency (increased fetal erythropoiesis secondary to chronic intrauterine hypoxia):
    - Small-for-gestational-age infants
    - Maternal hypertension
    - Post-term infants
    - Infants born to mothers with chronic hypoxia (heart disease, pulmonary disease)
    - Maternal smoking
- Infants of diabetic mothers (increased erythropoiesis)
- Some Large-for-Gestational-Age (LGA) infants
- Dehydration of infants
- Infants with:
    - Beckwith-Wiedemann syndrome
    - Neonatal thyrotoxicosis
    - Congenital hypothyroidism
    - Trisomy 21

Clinical findings

- Many affected infants are asymptomatic.
- CNS: Poor feeding, lethargy, hypotonia, apnea, seizures, and cerebral venous thrombosis.
- Cardio-respiratory: Cyanosis, tachypnea, heart murmurs, congestive heart failure, cardiomegaly, increased pulmonary vascular resistance, prominent vascular markings on X-ray chest.
- Renal: Renal vein thrombosis, hematuria, oliguria
- Other: Increased jaundice, persistent hypoglycemia, necrotizing enterocolitis, DIC.

Diagnosis

- Polycythemia is diagnosed when a central hematocrit is 65% or higher.
- Capillary blood or peripheral venous hematocrit level should be determined in any newborn who:
    - Appears plethoric
    - Has any predisposing cause of polycythemia
    - Has any of the symptoms mentioned in clinical features
    - Is not well for any reason

Management

- Asymptomatic infants with a peripheral venous hematocrit between 65–70% can be managed by:
    - Increasing fluid intake one day ahead of requirement
    - Continue observation and epeat the hematocrit in 4–6 hours
- Symptomatic infants should have a partial exchange transfusion if the peripheral venous hematocrit is more than 65%.
- The following formula is used to calculate the exchange normal saline:

  Volume of exchange (ml) = observed hematocrit-desired hematocrit x body weight (kg) x 80 ml/observed hematocrit

  OR Volume to be exchanged= 20ml/kg

Prognosis

- Infants treated with partial exchange transfusion are at increased risk of necrotizing enterocolitis.
- Most infants develop normally.

NEONATAL THROMBOCYTOPENIC PURPURA

CASE

A newborn baby girl is born by Spontaneous Vaginal Delivery (SVD) at term. At birth, there is a ***generalized petechial rash*** and minor bruising. Examination is ***otherwise normal***. There is ***no hepatosplenomegaly*** and radii are present. There are no risk factors for sepsis. A complete blood count reveals a normal WBC count with differential. Hemoglobin is 17 g/dL; and platelet count 11,000/mm^3 (***thrombocytopenia***) with large platelets present.

- Neonatal thrombocytopenia is a platelet count of less than 150,000/mm^3.
- It accounts for 2–3% of healthy and 20–30% of sick neonates.

Causes

- Increased consumption
    - Autoimmune thrombocytopenia

  - Alloimmune thrombocytopenia
- Decreased production.
  - Thrombocytopenia with absent radii (TAR).
  - Placental insufficiency
  - IUGR
  - NEC
  - Birth Asphyxia
- Consumption may be caused by:
  - Infections/sepsis, TORCH, group B streptococcus, Listeria monocytogenes, E.coli, CMV
  - Mechanical problems
  - Intravascular coagulation
  - Bernard-Soulier syndrome
- Most causes are generally self resolved. More serious thrombocytopenia (<20,000/mm^3) needs evaluation and intervention.
- In sick neonates, the condition resolves with treatment of primary disease.

Diagnosis

Maternal history

- History of thrombocytopenia
- Bleeding before or during pregnancy
- A previous splenectomy
- Drug use
- Infection

Infant

- Baby may be healthy or may appear sick
- Petechiae or large bruises
- Hepatosplenomegaly
- Jaundice
- Hemangioma

Table 9.17: Clinical statuses in neonatal thrombocytopenia.

Sick infant with decreased platelet count	
Normal PT, APTT	**PT, APTT increased**
Infection (without DIC) Hypersplenism Marrow infiltration Necrotizing enterocolitis	DIC Sepsis Hypoxia Acidosis Cold stress Severe liver disease
Healthy infant with decreased platelet count	
Mother's platelet count normal	**Mother's platelets decreased**
Neonatal allo-immune thrombocytopenia. Neonatal drug	Maternal ITP Maternal drug Familial

Laboratory studies

- Maternal platelets count (platelet typing if the maternal count is normal).
- Baby: CBC, platelets count, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT).

Management

Platelet transfusion

- Indications:
  1. Bleeding
  2. Platelets count <20,000/mm^3
- Donor should not be mother (use a random donor), except for the infant with allo-immune thrombocytopenia. In this, case, the maternal platelets after appropriate testing may be used.
- 10-20ml/kg of platelets transfusion raises the platelet count by 50,000 to 100,000/ml, unless there is peripheral destruction of the platelets.
- Normal half-life of platelets is 4–5 days. It is shorter if there is increased platelet consumption.
- Never give platelets through an arterial or umbilical line because thrombosis may occur.

Whole blood transfusion

- In an emergency, whole blood may be used for exchange transfusion.

IMMUNE THROMBOCYTOPENIA:

- In Immune Thrombocytopenias (ITP), maternal antibody crosses the placenta, resulting in destruction of neonatal platelets.
- It is called **auto-immune** when the antibody is directed against an antigen on the mother's own platelets shared in common with the baby's platelets.
- It is called **allo-immune** when antibodies are directed against antigens on the baby's platelets but not against antigens on the maternal platelets.

Auto-immune Thrombocytopenia (auto- [illegible]

- Various autoimmune syndromes (e.g. SLE) may cause autoimmune thrombocytopenia.
- Mother is suffering from ITP or has low platelet count during current pregnancy or in the past.

Pathophysiology

- Maternal autoantibodies passively cross the placenta and bind to neonatal platelets.
- A normal maternal platelet count does not rule out this cause.
- There may be a maternal history of thrombocytopenia or symptoms of autoimmune syndromes (SLE).
- Maternal thrombocytopenia at delivery is common.
- Almost all infants born to women with thrombocytopenia are either unaffected or have mild to moderate thrombocytopenia that is self-resolving. It does not result in intracranial hemorrhage.

Clinical findings

- Infant usually has mild to moderate thrombocytopenia (20,000–50,000) and is usually healthy.
- There are petechiae or bruises.
- There may be increased bruising at the injection site or bleeding at circumcision.
- Mother usually has thrombocytopenia or a history of ITP.

Management

Prenatal treatment

- Deltacortil is given to mothers with ITP. Dose is 10–20 mg given for 10–14 days before delivery.
- Cesarean section reduces trauma to the infant and decreases the risk of bleeding.

Postnatal treatment

- Send cord blood sample right after birth. Check platelets counts daily for first 3-4days or until platelets counts are above 100,000
- If Platelets counts are <25,000whether bleeding or not treat with IVIG and or steroids.

Allo-immune thrombocytopenia

- It is under-diagnosed condition occurring in 1:1000 births.
- The thrombocytopenia is caused by maternal sensitization to paternal antigens present on fetal platelets.
- Maternal antibodies cross the placenta and destroy fetal platelets like Rh sensitization. But the first child can be affected in this condition.

Clinical findings

- The infant appears healthy but has petechiae, bruising, bleeding, and a low platelet count (<20,000).
- Mother has a normal platelet count.
- There may be a history of previously affected pregnancy.
- Intracranial hemorrhage is the most serious complication occurring in 10–20% of cases.

Management

Prenatal treatment

- Intravenous gamma globulin (1-2 gm/kg/week).+/- Steroids (prednisolone 0.5–1 mg/kg/day) started at 12 or at 20weeks to 26 weeks of gestation.
- Prenatal platelet transfusion by percutaneous umbilical blood sampling (PUBS) can be given in severe cases.
- Elective cesarean section.

Postnatal treatment

- Platelet transfusion: If the newborn baby has a platelets count of less than 30,000/ml, or if the baby shows any signs of bleeding, the mother's platelets are transfused into the baby. Plateletsshould be random donor particularly HPA compatible. or
- Intravenous gamma globulin (IVIG) 1g/kg BID for 3–5 days.
- Steroids: Methylprenisolone is given to newborns with continued low platelet counts and does not respond to plateletstransfusion and IVIG.

Prognosis

- About 20% of all infants with neonatal alloimmune thrombocytopenia have intracranial hemorrhages.
- Cranial ultrasound study is indicated after delivery since intracranial hemorrhages are sometimes clinically silent.

BIRTH (TRAUMA) INJURIES

CASE

A 5-hour-old newborn presents with history of lethargy after prolonged and obstructed labor. His weight is 4 kg. There is decreased movement in right arm and is pronated.

- Most commonly birth trauma occurs with:
    - Difficult delivery.
    - Increased fetal weight
    - Abnormal fetal position
    - Fetal distress requiring rapid extraction with forceps or vacuum

Clinical findings

- Head injuries (scalp bruising, scalp edema, cephalohematoma usually beneath the parietal periosteum, subgaleal hematoma). Severe injury can cause massive blood loss, shock, brain injury and death.
- Brain injury (subdural or subarachnoid bleeding causes alternating somnolence and irritability, poor eating, unexplained fevers.
- Bone injury (fractures of clavicle, humerus, femur, and zygomatic arch are most common).
- Cervical-brachial plexus injury (usually unilateral paresis due to damage to cervical roots C5–6 or C8–T1).
- Facial nerve injury (intrauterine pressure of fetal head against maternal sacrum or forceps application causes asymmetrical mouth during crying and poor eye closure on affected side).
- Cervical spinal cord injury (flaccid paresis or paralysis with normal facial tone).

Differential diagnosis

- Clinical findings may reflect respiratory, cardiac, or muscle disease
- Metabolic disease
- Neurologic disease

- Brain malformation
- Sepsis
- Hypoglycemia

Management

- Caput succedaneum, cephalohematoma, bruises (observe for possible elevations of bilirubin and for anemia)
- Nerve injury (physiotherapy)
- Fractures (splinting and analgesia)
- Subdural hemorrhage (drain only if there are signs of increased intracranial pressure)
- Subgaleal hemorrhage—intensive care, blood, and clotting factor replacement

Prognosis

- Birth-related nerve injuries often improve rapidly, but long-term resolution may be incomplete.

NEONATAL CONJUNCTIVITIS

- Neonatal conjunctivitis presents during the first month of life. It may be aseptic or septic.
- Aseptic neonatal conjunctivitis most often is a chemical conjunctivitis that is induced by silver nitrate solution, which is used for prophylaxis of infectious conjunctivitis.
- Bacterial and viral infections are major causes of septic neonatal conjunctivitis, with *Chlamydia* being the most common infectious agent. Infants may acquire these infective agents as they pass through the birth canal during the birth process.

Chlamydial conjunctivitis

- *Chlamydia trachomatis* is an obligate intracellular bacteria and has been identified as the most common infectious cause of neonatal conjunctivitis.
- The reservoir of the organism is the maternal cervix or urethra. Infants who are born to infected mothers are at high risk (approximately 25–50%) for developing an infection.

Neisserial conjunctivitis

- *Neisseria gonorrhoeae* is a gram-negative diplococcus.
- It is potentially the most dangerous and virulent infectious cause of neonatal conjunctivitis.
- The reservoir of *N.gonorrhoeae* is the mother of the infant and is acquired during birth.
- Gonococci can penetrate intact epithelial cells and divide rapidly inside them.

Other bacteria

- The most commonly identified gram-positive organisms include *Staphylococcus aureus*, *Streptococcus pneumonia*, *Streptococcus viridans*, and *Staphylococcus epidermidis*. These bacteria make up 30–50% of all cases of neonatal conjunctivitis.

Herpes simplex

- Herpes Simplex Virus (HSV) can cause neonatal keratoconjunctivitis, but it is rare (<1%) and can be associated with a generalized herpes simplex infection.

Incubation period

- Chemical conjunctivitis secondary to silver nitrate solution application usually occurs in the first day of life, disappearing spontaneously within 2–4 days.
- Gonococcal conjunctivitis tends to occur 2–7 days after birth but can present later.
- Chlamydial conjunctivitis usually has a later onset than gonococcal conjunctivitis; the incubation period is 5–14 days.

Clinical presentation of gonococcal conjunctivitis

- Conjunctivitis starting 1–4 days after birth.
- Gonococcal conjunctivitis tends to be more severe than other causes of ophthalmia neonatorum; there is a classic presentation of bilateral purulent conjunctivitis.
- Corneal involvement, including diffuse epithelial edema and ulceration, may progress to perforation of the cornea and endophthalmitis.

Clinical presentation of chlamydial conjunctivitis

- Conjunctivitis usually appears 5–14 days after birth.
- The presentation of chlamydial conjunctivitis may range from mild hyperemia with scant mucoid discharge to eyelid swelling, chemosis, and pseudomembrane formation.
- Blindness, although rare and much slower to develop than in gonococcal conjunctivitis, is not due to corneal involvement as in gonococcal conjunctivitis; eyelid scarring and pannus (as in trachoma) cause it.

Management

Sticky eye/blocked tear duct

- 4–6 hrly eye toilet using sodium chloride 0.9%
- cooled, boiled tap water acceptable for home use

Conjunctivitis

- Swab all for:
  - Gram stain and bacterial culture and sensitivities
  - If other suspicions of HSV (e.g. vesicles etc.), swab in viral transport media for HSV PCR
  - swab in viral transport media (checks for Chlamydia trachomatis and Neisseria gonorrhoeae PCR)
  - Treat both eyes with:
  - frequent eye toilet as necessary
  - chloramphenicol 0.5% eye drops
  - fusidic acid 1% eye drops for staphylococcus
  - Presentation ≤24 hr of birth suggests gonococcal infection

SUBSEQUENT MANAGEMENT

- In severe non-resolving cases
    - Take throat and eye swabs for viral PCR
    - If herpes suspected, look for other signs of herpetic infection
    - Treat suspected herpes with aciclovir IV and topical for 14 days
    - Refer to ophthalmology
- Neisseria gonorrhoeae suspected
    - Request urgent Gram stain and culture
    - Swab in viral transport media for PCR
    - Assess baby for septicaemia
- Neisseria gonorrhoeae confirmed
    - Give single dose cefotaxime 100 mg/kg IV stat
    - For severe cases, frequent sodium chloride 0.9% irrigation of the eyes and continue treatment with
    - cefotaxime IV for up to 5 days
    - Refer to ophthalmology
    - If due to Neisseria gonorrhoea or chlamydia discuss referral to the genitourinary medicine services
- Chlamydia result positive
    - Treat with erythromycin 12.5 mg/kg oral 6-hrly for 14 days
- Gonococcal or chlamydia infection detected
    - Refer mother and partner to genitourinary medicine for immediate treatment
- Mother and father should be evaluated and treated for genital infection.

CHAPTER 10

Infectious Diseases

ACUTE DIARRHEA

CASE

A one-year-old child presents with green ***watery stools***. He also has ***vomiting*** and ***irritability*** for last one day. Physical examination shows fever, ***dry mucous membranes*** and ***sunken eyes***.

Definition

- Passage of three or more stools in a day, of consistency softer than usual for the child, or one watery stool is defined as diarrhea.

Incidence

- There are 3–4 episodes of diarrhea per child per year.
- Maximum incidence is in 1st year of life.
- It accounts for 40–50% of our hospital admissions during summer and rainy season.
- It causes an estimated 2.5lac deaths in children under five years of age per year as compared to United States in which approximately 125 deaths occur each year as a result of gastroenteritis.
- 40% of children in Pakistan are normally nourished and diarrhea is an important factor in the malnutrition of the rest.

Etiology

- Infections of the gastrointestinal tract are caused by a wide variety of enteropathogens, including bacteria, viruses, and parasites. Detail is given in the following table.

Table 10.1: Causative agents of gastroenteritis.

Bacteria	Escherichia coli (25%) Invasive Enterotoxic Entero-pathogenic Hemorrhagic (0157:H7) Salmonella (10%) Shigella (5%) Vibrio cholerae (5–10%) Staphylococcus aureus (food poisoning). Campylobacter jejuni Yersinia enterocolitica
Viruses	Rota virus (40%) Enteric adenovirus
Parasites	Entamoeba histolytica Giardia lamblia Cryptosporidium
Fungi	Candida albicans

Table 10.2: Miscellaneous and non-infectious causes of acute diarrhea.

Parenteral infections	Otitis media, Pneumonia, UTI
Dietary factors	Over-feeding, starvation Food poisoning Food allergy
Drugs	Antibiotics

Epidemiology

- Diarrhea is one of the leading causes of morbidity and mortality in children.
- The major mechanism of transmission for diarrheal organisms is feco oral, with contaminated food and water responsible for most of the episodes.
- Some entero-pathogens are infectious in a small inoculum and may be transmitted by person-to-person contact. Such organisms include Shigella, Escherichia coli 0157:H7, Giardia lamblia, or enteric viruses.
- Factors increasing susceptibility to diarrhea are:
  - Lack of breastfeeding
  - Exposure to unsanitary conditions
  - Ingestion of contaminated food or water
  - Malnutrition
  - Measles
  - Level of maternal education

Pathogenesis

- In diarrhea, there is excessive loss of water and electrolytes in stools.
- Mechanism of action is different by various organisms.

Enterotoxigenic E.Coli

- Diarrhea results from action of toxins released by the bacteria on the intestinal mucosa.
- These toxins are heat labile (LT) or heat stable (ST).
- The LT toxins bind to the epithelial surface of the enterocytes and activate adenyle cyclase system and there is accumulation of cyclic AMP causing massive

secretion of sodium and chloride in the gut lumen; glucose stimulated sodium absorption remains intact.

- Heat stable (ST) enterotoxin activates guanylate cyclase, which also increases secretory activity of gut. Recovery occurs by replacement of affected cells by regeneration in 2–5 days.

Entero-invasive (shigella and salmonella)

- These cause invasion of enterocytes and results in necrosis and ulcer formation leading to diarrhea with blood and mucus in the stool.
- It presents as fever, abdominal cramps and tenesmus, and small volume of bloody mucoid stools with many pus cells.

Disaccharidase deficiency (rota virus)

- It invades intestinal cells and alters their functioning and reproduction.
- The exact mechanism in Rota virus is not known. But towards the end of illness it causes shedding of mucosal cells with loss of disaccharidases.
- It manifests as osmotic diarrhea due to failure of digestion of lactose and other disaccharides.
- Recovery occurs when the mucosal surface regenerates.

Vibrio cholerae

- They adhere to and multiply on the mucosa of small intestine and produce heat labile enterotoxin, which attaches to a receptor (GM1 ganglioside) on gut epithelium.
- It activates adenylate cyclase to produce increased amount of cyclic AMP, which causes decreased absorption of sodium and chloride resulting in water and electrolyte loss.

Evaluation of the patient with acute diarrhea

History

- Presenting complaints (loose motions, vomiting, fever, etc)
- Loose motions (duration, frequency, grade, blood in stool, mucus in stool). Color of stool (rice water in cholera)
- Vomiting (duration, frequency, relation with food, nature, quantity, color, blood in vomiting)
- Fever (duration, low or high grade)
- Any associated illness (cough in acute respiratory infection, rash in measles, urinary complaints in UTI)
- Urine (passed or not within last 6 hours, quantity)
- Abdominal pain or distension
- Any history of seizures
- Past history of diarrhea
- Treatment given previously (especially antibiotics, antidiarrheals, or ORS)

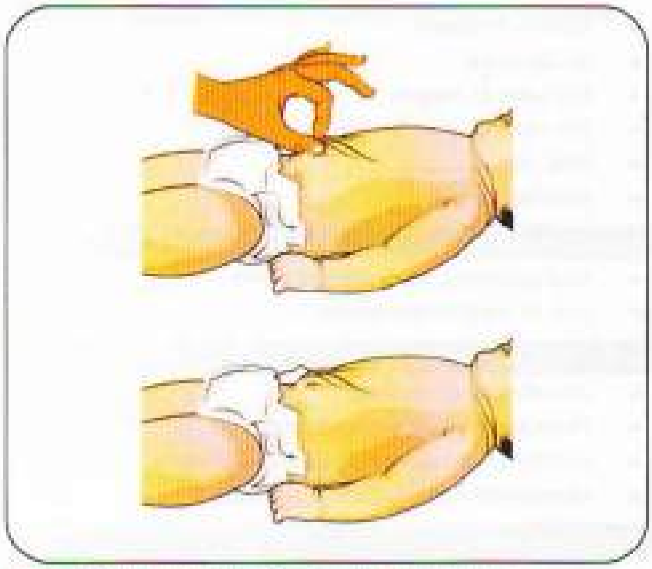


Figure 10.1: Illustration to examine skin turgor.

- Feeding history (breast fed or not, duration of breastfeeding, type of top feeding, feed given by feeder or cup and spoon, quantity of feeding in 24 hours, dilution, level of sterilization of utensils). Weaning history (when started, type of weaning, amount of weaning food).
- Developmental history
- Vaccination history
- History of contact with a tuberculous or measles patient
- Social and family history

Examination

- General behavior (drowsy, irritable)
- General physical examination (pulse, temperature, respiratory rate, blood pressure or skin perfusion, weight)
- Mucous membranes (normal, dry, parched)
- Skin turgor (normal, lost, goes back slowly, goes back very slowly)
- Eyes (normal shiny with tears, not sunken, sunken, cornea hazy)
- Anterior fontanel (open, closed, depresses, full or bulging)
- Abdomen (normal, distended, any mass palpable, bowel sounds)
- CNS, and respiratory system examination to find any associated abnormality

Pathophysiology

- Dehydration results from loss of water and electrolytes
- Following are the effects of diarrhea.

Loss of water

- Loss of skin turgor
- Weak or absent pulse
- Tachycardia
- Sunken eyes

- Sunken fontanel
- Husky voice
- Cyanosis of fingers
- Dry mucous membranes
- Cold skin
- Anuria, uremia

Loss of nutrients

- Hypoglycemia, convulsions, coma
- Loss of weight–marasmus

Loss of bicarbonate

- Vomiting and retching
- Deep and sighing respiration
- Irritability–increased O_2 demand of brain
- Myocardial contractility is decreased

Potassium loss

- Abdominal distension, paralytic ileus
- Sustained shock

Classification of dehydration

Clinical

- **Mild:** When weight loss is less than 5%
- **Moderate:** When weight loss is between 5–10%
- **Severe:** When weight loss is more than 10%
- **Isotonic** (70% of cases): When serum sodium level is between 130–150 mmol/L
- **Hypotonic** (20% of cases): When serum sodium level is less than 130 mmol/L
- **Hypertonic** (10% of cases): When serum sodium level is more than 150 mmol/L

Clinical findings

- The onset is sudden with diarrhea and vomiting.
- The stools are large in volume, watery in consistency and usually green in color.
- Sudden loss of weight often precedes other clinical manifestations (if previous weight is known).
- Dehydration develops rapidly due to loss of body water and electrolytes in stools and vomiting.
- **In mild dehydration** infant is irritable and restless. Thirst is marked and feeds are taken eagerly but often vomited. Anterior fontanel is slightly depressed.
- **In moderate dehydration**, irritability is more marked; eyes and fontanel are sunken and skin wrinkles abnormally when pinched. The extremities feel cool and may be cyanosed. There may be metabolic acidosis with deep, rapid and sighing respiration. Thirst is usually marked.
- **In severe dehydration**, condition becomes critical due to oligemia and peripheral circulatory failure. The skin is cold and ashen grey, extremities are deeply cyanosed and the desire to suck has been lost. The corneae are glazed and the eyeballs are often rolled upwards. The fontanel is deeply sunken and urine output ceases.
- Acute diarrhea is usually a self-limited disease. Vomiting and fever usually resolves quickly but diarrhea persists for 3–4 days then gradually diminishes over another 4–5 days.

Grading of stools

- Stool consistency can be assessed by WHO grading and it helps in assessing the stool water loss.
- It is also helpful in assessing the prognosis, e.g. if stool grade increases from grade III to IV and then V, it means diarrhea is worsening and if grade reverses from grade V to IV then diarrhea is improving.

Table 10.3: Grading of stools.

Grade I	Normal formed stools
Grade II	Soft stools
Grade III	Liquid stools taking shape of the container
Grade IV	Watery stools with flakes, appears opaque in glass container
Grade V	Watery stools with few flakes, appears translucent in container

Oral rehydration salt (ORS)

- ORS (low or reduced osmolar) contains the following:

Table 10.4: Composition of WHO low osmolar ORS (total osmolarity is 245 mOsm/L).

Reduced Osmolality ORS	**GRAM/Litre**	**Reduced Osmolarity ORS**	**Mmol/l**
Sod.Chloride	2.6	Sodium	75
Potassium Chloride	1.5	Chloride	65
		Potassium	20
Trisodium Citrate, Dihydrate	2.9	Citrate	10
Glucose, Anhydrous	13.5	Glucose, Anhydrous	75
Total Weight	20.5	Total Osmolarity	245

- The absorption of sodium and water in small intestine is more rapid in presence of glucose.
- The potassium is important to prevent hypokalemia.
- The bicarbonate is absorbed to correct acidosis.
- The contents should not be boiled in water and fresh solution should be prepared each day.
- The solution can be given by a cup and spoon, feeding bottle or nasogastric tube.

- Vomiting may occur initially but it usually subsides without any medication. If vomiting occurs persistently then start IV therapy.

Investigations

- Blood counts
- Stool examination for:
  - pH and reducing substances
  - Giardia cysts and entamoeba
  - Bioassay for E. coli.
  - Leucocytes and RBCs
  - Culture and sensitivity
  - Elisa test (for Rota virus)
- Serum electrolytes (Na^+ and K^+) and bicarbonate (HCO_3).
- Urine examination and culture (for parenteral diarrhea)
- Blood culture (salmonellosis or shigellosis)
- X-ray chest (for pneumonia)

Complications

- Most of the complications associated with gastroenteritis are due to delays in diagnosis and delays in the institution of appropriate therapy.
  - Dehydration and shock.
  - Metabolic acidosis.
  - Paralytic ileus (hypokalemia).
  - Convulsions and coma (hypernatermia, cerebral thrombosis).
  - Malnutrition (long standing diarrhea).
  - Acute renal shut down.
  - Persistent diarrhea (disaccharidase deficiency).
  - Superadded infections.
  - Thrush.
  - Diaper dermatitis.
  - Sclerema.
  - DIC
  - Death

Table 10.5: Assessment of diarrhea for dehydration.

No Dehydration	*Some Dehydration*	*Severe Dehydration*
Not enough signs to classify as some or severe dehydration.	Two of the following signs: • Restless, irritable. • Sunken eyes. • Drinks eagerly, thirsty. • Skin pinch goes back slowly.	Two of the following signs: • Lethargic or unconscious. • Sunken eyes. • Not able to drink or drinking poorly. • Skin pinch goes back very slowly.
Treatment Plan A	*Treatment Plan B*	*Treatment Plan C*

Management

- Before starting therapy, we assess degree and type of dehydration according to the following plan:

Does the child have diarrhea?

If yes, ***ask***:

- For how long?
- Is there blood in the stool?

Look and ***Feel***:

- Look at the child's general condition.
  Is the child:
  - Lethargic or unconscious?
  - Restless and irritable?
- Look for sunken eyes.
- Offer the child fluid.
  Is the child:
  Not able to drink or drinking poorly? Drinking eagerly, thirsty?
- Pinch the skin of the abdomen.
  Does it go back:
  Very slowly (longer than 2 seconds)?
  Slowly?

Now classify diarrhea: (as given in the above table)

Treatment Plan A (for no dehydration)

Treat diarrhea at home

Counsel the mother on the 3 rules of home treatment: Give extra fluid, continue feeding and tell when to return.

1. Give Extra fluid (as much as the child will take)

a. **Tell the mother:**
   - Breastfeed frequently and for longer at each feed.
   - If the child is exclusively breastfed, give ORS or clean water in addition to breast milk.
   - If the child is not exclusively breastfed, give one or more of the following: ORS solution, food-based fluids (such as soup, rice water, and yoghurt drinks), or clean water.

   It is especially important to give ORS at home when:
   - The child has been treated with Plan B or Plan C during this visit.
   - The child cannot return to a clinic if the diarrhea gets worse.

b. **Teach the mother how to mix and give ORS. Give the mother 2 packets of ORS (1000 ml) to use at home.**

c. **Show the mother how much fluid to give in addition to the usual fluid intake:**

Up to 2 years	50 to 100 ml after each loose stool
2 years or more	100 to 200 ml after each loose stool

d. **Tell the mother to:**
   - Give frequent small sips from a cup.
   - If the child vomits, wait for 10 minutes. Then continue, but more slowly.

- Continue giving extra fluid until the diarrhea stops.

2. **Continue feeding**

- Continue to breast feed frequently.
- If the child is not breast fed, give cow's milk or formula milk half diluted for 2 days.
- If the child is 6 months or older or already taking solid food. After rehydration give freshly prepared food like cereal with pulses, vegetables, meat or fish. Give food at least 4–6 times a day.
- Give fresh fruit juice or mashed banana to provide potassium.

3. **When to return for follow up visit**

- Advise the mother to come after 5 days for follow-up.

4. **When to return immediately**

- Advise mother to return immediately if the child has any of these signs.

Table 10.6: Signs when the child should be referred to hospital.

Any sick child	• Not able to drink or breastfeed • Becomes sicker • Develops a fever
If the child has diarrhea, also return if:	• Blood in stool • Drinking poorly

Treatment plan B (for some dehydration)

Treat some dehydration with ORS

Tell the recommended amount of ORS over 4 hours period. Determine amount of ORS to give during first 4 hours.

Table 10.7: Amount of ORS to be given to the child.

Age	Weight	ORS in ml
Up to 4 months	<6 kg	200–400
4 months up to 12 months	6-<10 kg	400–700
12 months up to 2 years	10-<12 kg	700–900
2 years up to 5 years	12–19 kg	900–1400

Use the child's age only when you do not know the weight. The approximate amount of ORS required (in ml) can also be calculated by multiplying the child's weight (in kg) times 75.

- If the child wants more ORS than shown, give more.
- For infants under 6 months who are not breastfed, also give 100–200 ml clean water during this period.

Show the mother how to give ORS solution

- Give frequent small sips from a cup.
- If the child vomits, wait 10 minutes. Then continue, but more slowly.
- Continue breastfeeding whenever the child wants.

After 4 hours

- Reassess the child and classify the child for dehydration.
- Select the appropriate plan to continue treatment.
- Begin feeding the child in clinic.

If the mother must leave before completing

- Show her how to prepare ORS solution at home.
- Show her how much ORS to give to finish 4-hour treatment at home.
- Give her enough ORS packets to complete rehydration. Also, give her 2 packets as recommended in Plan A.
- Explain the 3 rules of home treatment.
    1. Give extra fluid.
    2. Continue feeding (as given in Plan A).
    3. When to return (as given in Plan A).

Treatment plan C (treat severe dehydration

1. Can you give intravenous (IV) fluid

➢ ***If Yes:***

- Start IV fluid immediately. Give 100 ml/kg Ringer's Lactate Solution (or, if not available, normal saline), divided as follows:

Table 10.8: Division of IV fluid.

Age	First give 30 ml/kg in:	Then give 70 ml/kg in:
Infants (under 12 months)	1 hour*	5 hours
Children (12 months up to 5 years)	30 minutes*	2 ½ hours

- (Repeat once if radial pulse is still very weak or not detectable).
- Reassess the child every 1–2 hours. If hydration status is not improving, give the IV drip more rapidly.
- Also give ORS (about 5 ml/kg/hour) as soon as the child can drink: Usually after 3–4 hours (infants) or 1–2 hours (children).
- Reassess an infant after 3 hours and a child after 6 hours. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment.

➢ **If you cannot give IV fluids**

2. Is IV treatment available nearby (within

➢ **If yes**

- Refer urgently to hospital for IV treatment.
- If the child can drink, provide the mother with ORS solution and show her how to give frequent sips during the trip.

➢ **If no treatment available nearby**

3. Are you trained to use a Nasogastric (NG) tube for rehydration?

- **If yes**
  - Start rehydration by tube (or mouth) with ORS solution: give 20 ml/kg/hour for 6 hours (total of 120 ml/kg).
  - Reassess the child every 1–2 hours. If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly. If hydration status is not improving after 3 hours, send the child for IV therapy.
  - After 6 hours, reassess the child. Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment.
- **If not trained to pass NG tube**
  - Refer urgently to hospital for IV or NG treatment.

Note: If possible, observe the child at least 6 hours after rehydration to be sure the mother can maintain hydration giving the child ORS solution by mouth.

Hospital management of severe dehydration

The basic principle of fluid therapy is to match output with input of water and electrolytes. Fluids are given to correct the following:

1. Deficit therapy

To correct existing water and electrolyte deficit.

2. Concurrent losses

Replacement of ongoing losses due to diarrhea and vomiting.

3. Maintenance therapy

Provision of normal daily fluid requirements. Intravenous therapy is indicated in following cases:

- Severe dehydration
- Shock
- Severe vomiting
- Abdominal distension

Intravenous route is established and fluid requirement is calculated as follows:

Deficit therapy = 100 ml/kg
Maintenance fluid = 100 ml/kg
Continuous losses = 25 to 50 ml/kg
Total fluid given = 100+100+50
= 250 ml/kg on 1st day

Then on subsequent days, give maintenance therapy and keep replacing ongoing losses till oral feeding is possible.

1. Fluids for deficit therapy

Give ***Ringer's solution or normal saline*** (100 ml/kg) as follows:

- In infants under 12 months of age:
  First give 30 ml/kg in 1 hour, then 70 ml/kg over the next 5 hours.
- *In children 12 months up to 5 years age:*
  First give 30 ml/kg in 30 minutes, then 70 ml/kg over the next 2 ½ hours.

If the child is in shock, push 20 ml/kg fluid in 10–15 minutes and then reassess the patient. Repeat the fluid 20 ml/kg in 10–15 minutes if the radial pulse is still very weak or not detectable. When patient is out of the shock, then give the fluid according to age as given above.

2. Fluid for concurrent losses

5% dextrose ½ saline is given 50–75 ml/kg in next 6–8 hours.

Fluid for maintenance therapy

5% dextrose 1/5 saline is given 100 ml/kg/day. If the child is able to drink, maintenance therapy may be given by ORS.

3. Electrolyte replacement

Potassium replacement is usually started when urinary flow has been established, i.e. in next 6–8 hours. Normal requirement is 2 mEq/kg/day. Potassium should be given in the drip and in not less than 6 hours. In 24 hours, no more than 40 mEq/l of potassium is given. Rapid injections of potassium may cause ventricular fibrillation and death.

Bicarbonate is given in severe metabolic acidosis. Give Sodium bicarbonate ($NaHCO_3$) start with 2 mEq/kg slow and diluted IV and repeat after 2 hours if required. Remaining amount is calculated from the formula and added to the drip.

$NaHCO_3$ (in mEq) = 0.5 × wt (kg) × (28–serum $NaHCO_3$)

Note

- Stool losses should be replaced with ½ saline (0.45%) 1 ml for 1 ml stool.
- For gastric aspiration add normal saline 1 ml for 1 ml.
- For fever add 20 ml/kg of 1/5 saline per degree rise of temperature.
- For hypokalemia add potassium 2 mEq/kg/day or 1–2 g KCl orally per day (1 g = 13 mEq).
- For newborns up to 2 weeks volume of fluid should be 2/3rd of above as 1/5 dextrose saline.
- For malnourished, give 2/3rd dextrose saline (100 mEq/l of Na^+) IV, blood or plasma. Magnesium sulfate is also given 1 ml twice a day for 3 days.

4. Antibiotics

Antibiotic cover is essential in patients where diarrhea is known to be bacterial or protozoal. Anti-diarrheal agents are not recommended. Antibiotics in the treatment of diarrhea are given in table 10.9 below.

5. Dietary management

There is no physiological basis to rest the bowel during diarrhea. Feeding should be continued to prevent body catabolism and weight loss.

Breast-fed infants should be allowed to breast feed as often as the infant desires in addition to ORS.

Bottle-fed infants: Ratio of ORS to other fluids should be *2:1 (2 parts of ORS and 1 part milk or other fluids).*

In addition, children older than 4–6 months should eat food that provides adequate calories and is easily digestible.

Zinc supplementation

- Zinc supplementation in children with diarrhea leads to reduced duration and severity of diarrhea.
- It prevents diarrhea from recurring.
- Zinc administration in acute diarrhea can significantly reduce mortality and repeated hospital admission.
- Zinc administration also improves diarrhea recovery rates.

Table 10.9: Antibiotics chosen to the at different causes.

Cause	Antibiotic of choice
Cholera	• Tetracycline 50 mg/kg/day PO in 4 divided doses for 2 days. • Furazolidine 5 mg/kg/day PO in 4 divided doses for 3 days.
Shigella	• Ceftriaxone 50–100 mg/kg/day IV or IM, qd or bid for 7 days • Ciprofloxacin 20–30 mg/kg/day PO bid for 7–10 days • Ampicillin PO, IV 50–100 mg/kg/day qid for 7 days
Amebiasis	• Metronidazole PO 30–40 mg/kg/day tid for 7–10 days
Giardiasis	• Furazolidone PO 25 mg/kg/day qid for 5–7 days • Metronidazole PO 30–40 mg/kg/day tid for 7 days • Albendazole PO 200 mg bid for 10 days

- All children older than 6 months of age with acute diarrhea should receive oral zinc (20 mg/day) for 10–14 days during and continued after diarrhea.

Prevention

Promotion of exclusive breastfeeding

- Exclusive breastfeeding means administration of no other fluids or food for the 1st 6 months of life.
- Exclusive breastfeeding protects infants from diarrheal disease. It promotes passive immunity and reduces the intake of potentially contaminated food and water.
- Breast milk contains all the nutrients needed in early infancy, and diminishes the adverse impact of diarrhea on nutritional status of infant.

Improved complementary feeding practices

- Appropriate complementary feedings in diarrhea decreases mortality in children age 6–11 months.
- Complementary food should be introduced at 6 months of age, and breastfeeding should be continued for up to 2 years of age.

Rotavirus immunization

- Rotavirus and cholera vaccines have a major effect on reducing diarrhea mortality.

Improved case management of diarrhea

- Prompt identification and appropriate therapy of diarrhea significantly reduces duration of diarrhea, malnutrition, and risk of death in childhood.
- WHO/UNICEF recommendations to use low-osmolality ORS, zinc supplementation for the management of diarrhea, and appropriate use of antibiotics (through IMCI) have reduced the number of diarrheal deaths among children.

Hypernatremic dehydration

- It is the most dangerous form of dehydration because it can cause serious neurologic damage by moving water out of the brain cells into hypertonic extracellular fluid.
- It results in brain cell shrinkage and tearing of blood vessels and in addition may cause hemorrhages and thrombosis.
- The child may be lethargic or irritable and may have fever, hypertonicity and hyperreflexia or seizures.
- Idiogenic molecules are generated within the brain cell which give it protection by increasing osmolality and protect against brain cell shrinkage. Overly rapid treatment lower the extracellular osmolality and cause water to move into the cells of brain producing cerebral edema, seizures, brain herniation and death.
- To minimize the risk of cerebral edema, serum Na should not decrease by >12 mEq/L every 24 hours. The fluid deficit should be corrected over 2–4 days. Initial resuscitation should be done with normal saline followed by 5% dextrose ½ normal saline with vigilant monitoring of sodium concentration.
- The patient should receive 1.25–1.5 times the normal maintenance fluid. ORS may be given cautiously if stable and patient has voided urine.
- Potassium is added to the fluids according to serum levels. Ringer's lactate should not be given and infant formula should be given cautiously as it has low sodium concentration.

CHOLERA

CASE

A child of 3 years age presents with ***acute*** onset of severe diarrhea and vomiting. ***Stools*** are ***watery***. There is ***severe dehydration***. There is no fever.

- Cholera is an acute dehydrating diarrheal disease caused by the gram-negative organism *Vibrio cholerae*.
- Cholera can rapidly lead to death, if appropriate treatment is not immediately started.

- It is transmitted by contaminated water or food (fecal-oral route).
- Mainly serotype O1 or serotype O139 (Bengal strain) are involved.
- Humans are the only known natural hosts.
- Breast milk plays a role in protecting children from severe cholera during the first 2 years of life.
- Nutritional status is an important factor determining the severity of the diarrhea.
- Duration of diarrhea is prolonged in children suffering from severe malnutrition.
- The incubation period is short, usually 6 hours to 5 days (average 2–3 days).

Pathophysiology

- Gastric acid is an important barrier in preventing the vibrios from reaching the small intestine because these organisms are very acid sensitive.
- To cause cholera, vibrios must colonize the small intestine, attach to small intestinal mucosa and proliferate.
- Cholera enterotoxin binds to a regulatory subunit of adenyl cyclase in enterocytes, causing increased cAMP. The high cAMP causes an increase in active secretion of chloride by crypt cells and a decrease in active absorption of sodium and chloride by villous cells.
- The fluid lost is isotonic with plasma and has high concentrations of bicarbonate and potassium.
- *V. cholera* has been shown to produce a second toxin known as 'zonula occludens toxin' (ZOT). This impairs the integrity of the tight junctions between enterocytes, allowing escape of water and electrolytes.
- A third toxin, 'accessory cholera enterotoxin' (ACE), which also increases the intestinal secretions, has been identified.

Clinical findings

- Asymptomatic infection is more common than clinical disease.
- Incubation period is 1–3 days (range is several hours to 5 days).
- Many patients infected with *V. cholera* have mild disease, with 1–2% developing severe diarrhea.
- Patient presents with vomiting that rapidly leads to hypovolemic shock, metabolic acidosis, and death.
- Diarrhea can progress to painless purging of profuse rice-water stools (suspended flecks of mucus) with a fishy smell, which is the hallmark of the disease.
- Low-grade fever occurs in some children.
- Vomiting may be projectile and is not accompanied by nausea.
- Within 2–3 hours, the massive loss of fluid and electrolytes results in life-threatening dehydration (sunken eyes, depressed fontanel, lost skin turgor, extreme thirst, and diminished urine output), with marked weakness and collapse (cold clammy skin, tachycardia, hypotension and peripheral cyanosis).
- If fluid therapy is not initiated, renal failure with uremia will occur, and death rapidly ensues.
- The illness lasts 1–7 days and is shortened by appropriate antibiotic therapy.
- **Cholera gravis:**
    - It is the most severe form of the disease.
    - It results when purging rates of 500–1,000 ml/hour occur.
    - This amount of purging leads to dehydration.
    - This is manifested by decreased urine output, a sunken fontanel in infants, sunken eyes, absence of tears, dry oral mucosa, poor skin turgor, thready pulse, tachycardia, hypotension, and vascular collapse.
    - Metabolic acidosis presents with typical Kussmaul breathing.
    - Patients may rapidly progress to coma.
    - Death can occur within hours if fluid losses are not corrected rapidly.

Complications

- Lethargy, seizures, altered consciousness, fever, hypoglycemia and death.
- Acute renal failure due to acute tubular necrosis.
- Hypokalemia and acidosis; hypokalemic arrhythmia leading to sudden death.
- Paralytic ileus and abdominal distension due to hypokalemia.
- Pulmonary edema during rapid fluid correction.
- Transient tetany during correction of electrolyte imbalance.

Diagnosis

- Diagnosis is mainly clinical.
- In endemic areas, any child with severe, watery diarrhea should be considered a possible case of cholera until confirmed by laboratory investigations.
- There may be marked acidosis, hypochloremia, hyponatremia, hypokalemia and hypoglycemia.
- Stool examination reveals few fecal leukocytes and erythrocytes because cholera does not cause inflammation.
- Microbiologic isolation of *V. cholerae* remains the gold standard for diagnosis.
- On stool microscopy, the characteristic darting motility of *vibrios* can be recognized in fresh wet preparations. To confirm these motile bacteria are *V. cholerae*, serogroup O1 antisera can be applied to wet preparations; immobilizing the organisms is a rapid and specific diagnostic test.
- Diagnosis is confirmed by stool culture.

Differential diagnosis

- Cholera occurs in large outbreaks which differentiate it from other diarrheal diseases.

- Diarrhea caused by enterotoxiganic *Escherichia coli* or rotavirus.

Management

- The mainstay of treatment for cholera is fluid (rehydration) and electrolyte replacement.

Oral rehydration

- Rice-based ORS is superior to standard ORS in children with cholera.
- Oral rehydration (ORS) given is the treatment of choice (100 ml/kg in 4 hours). Vomiting is not a contraindication to oral rehydration.
- ORS can be given as much a patient can take.
- Close monitoring is necessary, especially during the first 24 hours of illness, when large amounts of stool may be passed. After rehydration, patients have to be reassessed every 1–2 hours, or more frequently if profuse diarrhea is ongoing. Feeding should not be withheld during diarrhea. Frequent, small feedings are better tolerated than less-frequent, large feedings.

Intravenous rehydration

- If the child is not able to take oral fluids, has an ileus, or is in shock, IV fluids (Dextrose saline or Ringer's lactate) are given. Push 20 ml/kg of Dextrose saline or Ringer's lactate IV in 10–15 minutes and repeat if shock is not corrected.
- After correcting the shock, give 100 ml/kg Ringer's lactate or Dextrose saline in 2–3 hours to correct dehydration. Continue rehydration with Plabolyte-M till diarrhea persists.
- When urine is passed, add potassium chloride 2 ml/100 ml of Ringer's lactate or dextrose saline.
- All fluids should have glucose to prevent hypoglycemia.
- Food should be restarted as soon as fluid deficits are replaced. It will minimize nutritional impact of the illness.

Antibiotics

- Antibiotics are given to shorten the duration of illness, to reduce the period of excretion of organisms and to decrease the requirements of fluid replacement.
    - Erythromycin 12.5 mg/kg/dose 4 times a day for 3 days (up to 500 mg per dose for 3 days).*Or*
    - Azithromycin, 20 mg/kg as a single dose (up to 1 g).
    - Ciprofloxacin 20 mg/kg PO as a single dose.*Or*
    - Doxycycline 2–4 mg/kg PO as a single dose.
- Cephalosporins and aminoglycosides are not clinically effective against cholera.
- Zinc as supplement should be given as soon as vomiting stops.
    - Zinc supplementation shortens the duration of diarrhea and reduces subsequent diarrhea episodes.
    - Children younger than 6 months of age are given 10 mg of or al zinc, and children older than 6 months are given 20 mg of oral zinc daily for 2 weeks.

Prevention

- Most important method of preventing life-threatening cholera in infants is prolonged breastfeeding.
- Hand washing, safe food and water supply and proper handling of sewage are important preventive measures. In endemic areas, water and milk must be boiled, food protected from flies, and sanitary precautions observed.
- All patients with cholera should be isolated.
- Cholera vaccine provides 50% efficacy up to 3–6 months after vaccination.

Prognosis

- In children, the case fatality rate is 1–2%, even with early and rapid replacement of fluids and electrolytes.
- The mortality rate is over 50% if significant symptoms appear and no treatment is given.

SHIGELLOSIS (BACILLARY DYSENTERY)

CASE

A 2-year-old boy presents with ***crampy abdominal pain*** and ***grossly bloody diarrheal stool***. There is history of a brief ***seizure***. There is ***high-grade fever*** (104°F). Abdominal examination is normal.

Definition

- Acute diarrhea associated with blood, mucus and pus cells (WBCs) in the stool, is called dysentery.
- The term bacillary dysentery is used to describe dysentery caused by *shigellae*.

Etiology

- Shigellae are non-motile, gram-negative rods.
- There are four main types of shigella:
    1. S. dysenteriae (group A)
    2. S. flexneri (group B)
    3. S. boydii (group C)
    4. S. sonnei (group D)

Epidemiology

- Shigellosis is a common disease occurring primarily in children between 1–10 years of age. Fecal-oral transmission is more common in this age group.
- Infection in the first 6 months of age is rare especially in breast-fed babies.
- Humans are the major reservoir of infection.
- Contaminated food and water supplies are common source of spread.

- Incubation period is from 1–7 days (average 2–4 days). Infected patients, especially who are not receiving antibiotic therapy, may shed organisms up to a month.

Pathogenesis

- *Shigellae* are invasive pathogens that destroy the superficial epithelial cells, producing inflammation, edema, micro-abscesses, and ulceration with bleeding.
- The colon is selectively affected.

Clinical findings

- Onset may be abrupt.
- Child may have crampy abdominal pain, urgency, tenesmus, malaise, and non-localized lower abdominal tenderness.
- Temperature is usually up to 104°F (40°C) lasting for 1–3 days.
- Due to vomiting and diarrhea, there is dehydration.
- Watery and mucoid stools contain blood.
- Shigellosis may present like CNS disease such as meningitis, particularly when high-grade fever is associated with seizures, lethargy, and neck rigidity. Seizures occur in 30% of children with shigella gastroenteritis and are more common if the temperature rises up to 104°F.
- Symptoms generally last 3–7 days.

Investigations

- Stool examination should reveal leukocytes (pus cells) and red blood cells.
- Complete blood count may show leukocytosis with shift to left.
- In children who appear to be toxic, blood culture may be positive.
- Diagnosis is confirmed by isolating the *shigellae* by stool culture.

Complications

- Dehydration, acidosis, shock and renal failure
- Bacteremia, metastatic infections
- Febrile seizures
- Rectal prolapse
- Hemolytic-uremic syndrome

Differential diagnosis

- Other organisms causing dysentery are:
    - Entero-invasive *E.coli*
    - *Entamoeba histolytica*
    - *Campylobacter jejuni*
    - *Yersinia enterocolitica*
    - *Salmonellae*
- Other conditions mimicking shigellosis are:
    - Inflammatory bowel disease
    - Intussusception

Management

- Fluid and electrolyte replacement by using oral rehydration solution (ORS).
- Nutrition is a key concern, high-protein and high-caloric diet.
- A single large dose of vitamin A (200,000 IU) decreases the severity of shigellosis.
- Zinc supplementation (20 mg elemental zinc for 14 days) decreases the duration of diarrhea, improves weight gain and immune response, and decreases diarrheal disease in the next 6 months in malnourished children.
- Antibiotics not only cure the disease but also decrease further intestinal shedding of the organisms and further transmission of infection to others.
- Choice of antibiotics depends upon recent local stool culture reports.
- All antibiotics are given for 5 days.
- Effective antibiotics are nalidixic acid, ceftriaxone, ciprofloxacin, cefixime, chloramphenicol and azithromycin.
    - Ceftriaxone (50 mg/kg/24 hours as a single daily dose IV or IM).
    - The oral third-generation cephalosporin cefixime (8 mg/kg/24 hours divided every 12–24 hours).
    - Nalidixic acid (55 mg/kg/24 hours orally divided 4 times/day).
    - Azithromycin (12 mg/kg/24 hours orally for the 1st day, followed by 6 mg/kg/24 hours for the next 4 days).
    - Ciprofloxacin (20–30 mg/kg/24 hours divided into 2 doses) is the drug of choice recommended by the World Health Organization for bloody diarrhea.

Prevention

- Encourage prolonged breastfeeding.
- Hand washing especially after defecation and before food preparation and consumption should be done.
- Proper water and sewage treatment should be ensured.

Prognosis

- Prognosis is excellent if dehydration is treated adequately by fluid therapy.
- The mortality rate is high in very young, malnourished infants who do not receive fluid and electrolyte therapy.
- Antibiotic treatment produces a bacteriologic cure in 80% of cases after 48 hours of treatment.

PERSISTENT DIARRHEA

Definition

- An acute episode of diarrhea lasting more than 14 days and thought to be caused by infection is termed persistent diarrhea.
- It is estimated that only 5–15% of episodes of acute diarrhea last longer than 14 days.

- However, the mortality is higher (case fatality of persistent diarrhea is 5–7%, compared to 1% in acute diarrhea).
- Also 30–50% of all deaths from diarrhea occur due to persistent diarrhea.

Etiology

Infectious agents

a. Bacteria

- E.coli
- Shigella
- Salmonella (Non-typhoid)
- Campylobacter Jejuni

b. Protozoa

- Giardia lamblia
- Entameba histolytica

c. Fungi

- Cryptosporidium

Host factor

- Repeated episodes of diarrhea
- Improperly treated acute episode of diarrhea
- Malnutrition
- Lactose intolerance secondary to acute episode

Investigations

- Stool for culture, examination, pH, reducing substances.
- Electrolyte levels (especially Na_+, K^+).
- Complete blood count.

Management

- Rehydration: Where possible use ORS. Intravenous fluids may be needed.
- Nutritional rehabilitation:
  - Continue breastfeeding
  - Small, frequent meals of high nutrient value
  - Yogurt and khichri
  - Soya-based formula in special instances
  - Add Vitamin A, B_{12}, Zinc, Folate, and Iron
- Antibiotics: Use only in case of shigella.

GIARDIASIS

- Giardiasis is the most common protozoal cause of chronic relapsing diarrhea in children.
- It is caused by *Giardia lamblia*.
- It spreads from person to person or from contaminated water.
- Although infection is rare in neonates, it may occur at any age.
- The cysts are ingested and are the infectious form. The trophozoites are liberated after ingestion and are responsible for symptoms.
- Giardiae live in the duodenum.

Clinical findings

- Diarrhea due to *G. lamblia* is characterized by watery stools without blood, mucus, eosinophils, or leukocytes.
- Acute diarrhea occurs 1–2 weeks after infection and is characterized by abrupt onset of diarrhea with greasy, malodorous stools, malaise, flatulence, bloating and nausea. Fever is usually absent.
- Children who develop chronic diarrhea complain of profound malaise, lassitude, headache, and diffuse abdominal pain in association with bouts of diarrhea (most typically foul-smelling, greasy stools) with periods of constipation or normal bowel habits.
- Chronic diarrhea frequently leads to malabsorption, steatorrhea, vitamin A and iron deficiencies and secondary lactose intolerance.

Diagnosis

- Most commonly diagnosis is made by identification of the parasite (trophozoite or cyst) in fresh stool sample. Liquid stools have the highest yield of trophozoites.
- Detection of *Giardia* antigen in feces.
- Antigen assays detect *Giardia* by means of immunofluorescence or enzyme-linked immunoassay.

Management

- Metronidazole (15 mg/kg/day in three divided doses for 5 days) is the drug of choice for treatment of giardiasis in children.
- Tinidazole in children >3 years of age 50 mg/kg once.
- Nitazoxanide 1–3 years: 100 mg bid for 3 days, 4–11 years: 200 mg bid for 3 days.
- Albendazole in children >6 years: 400 mg once a day for 5 days
- Quinacrine 6 mg/kg/day in 3 divided doses for 5 days.
- For patients who fail one drug or suffer relapse, a second course with the same drug or changing to another drug is equally effective.
- Antigen assays detect *Giardia* by means of immunofluorescence or enzyme-linked immunoassay.

Prevention

- The prevention of giardiasis requires proper treatment of water supply and strict hand washing. Boil drinking water for over 10 minutes and avoid uncooked food.
- Treatment of both symptomatic and asymptomatic carriers may be necessary.

AMEBIASIS

CASE

A previously healthy 5-year-old boy presents with ***chronic diarrhea*** for 5 weeks. He has history of ***anorexia*** and ***abdominal cramps*** with abdominal distension. There is also history of ***loss of weight***. Stools are large and foul-smelling. There is no blood in stool.

- Amebiasis, caused by a protozoal parasite *Entamoeba histolytica*, is a common cause of acute dysentery and chronic non-dysenteric diarrhea.
- It may also cause hepatic and lung abscess.
- Transmission is usually fecal-oral, often from asymptomatic carriers who pass cysts.
- Trophozoites are killed by stomach acid and are not infectious.
- Once ingested, a cyst becomes a trophozoite in intestine that can cause invasive disease and produce characteristic flask-shaped ulcers in the intestinal mucosa.

Clinical findings

- Intestinal amebiasis can present as asymptomatic cyst passage, acute amebic proctocolitis, chronic nondysentric colitis or ameboma.
- Children with acute amebic colitis typically have a 1–2 week history of watery stools containing blood and mucus, abdominal pain and tenesmus.
- Some patients may be febrile or dehydrated.
- Abdominal examination may reveal pain over the lower abdominal quadrants.
- Chronic amebic colitis may present with recurrent episodes of bloody diarrhea over a period of years.
- Ameboma (a mass due to amebas), extra-intestinal lesions (lung, hepatic, brain abscesses), or intestinal perforation and hemorrhage may occur.

Diagnosis

Intestinal amebiasis is diagnosed by observing the parasite on fresh stool examination or mucosal biopsy. The presence of hematophagous trophozoites in feces indicates pathogenic *E. histolytica* infection. Stool examination for amebas is negative in more than half of patients with amebic liver abscess.

- Occult blood is present in almost all cases of amebic colitis; fecal leukocytes are uncommon in amebic dysentery
- Antigen detection test in stool
- Presence of antibodies against *Entamoeba.histolytica*.
- ELISA and indirect hemagglutination assays
- USG or CT scans for amebic abscesses

Differential diagnosis

- Colitis caused by bacterial (*Shigella*, *Salmonella*, enteropathogenic *Escherichia coli*, *Campylobacter*, *Yersinia*, *Clostridium difficile*), mycobacterial (tuberculosis and atypical mycobacteria), and viral (cytomegalovirus) pathogens
- Inflammatory bowel disease
- Pyogenic liver abscess from bacterial infection

Management

- Metronidazole (35–50 mg/kg/day in 3 divided doses for 7-10 days)
- Tinidazole (50–60 mg/kg/day once daily for 3 days)

For invasive (intraluminal) disease

- Metronidazole or Tinidazole followed by Paromomycin (25–35 mg/kg/day in 3 divided doses for 7 days) or Diloxanide furoate (20 mg/kg/day in 3 divided doses for 7 days) or Iodoquinol (30–40 mg/kg/day in 3 divided doses for 20 days)

Prevention

- Patients with amebiasis should be placed under enteric precautions.
- Strict hand washing and drinking boiled water and eating cooked or peeled vegetables and fruits.

TYPHOID (ENTERIC) FEVER

CASE

A 7-year-old girl, who recently traveled to a village with her family, presents with a 4-day history of ***continuousfever, diarrhea,*** and ***tenesmus*** and toxic look. There are palpable, small (2–4 mm) ***erythematous rash*** on the trunk only. Liver and spleen are enlarged. ***Stool examination*** reveals ***blood and leukocytes***.

- Typhoid fever is one of the commonest causes of PUO (Pyrexia of Unknown Origin).
- It is a bacterial disease caused by typhoid bacillus.
- It is characterized by prolonged fever, abdominal pain, diarrhea, delirium, rose spots, and splenomegaly and complicated sometimes by intestinal bleeding and perforation.

Etiology

- Typhoid fever is caused by *Salmonella typhi*.
- Para-typhoid fever is caused by *S. paratyphoid A*, *S. paratyphoid B (S. scottmuelleri)*, and *S. paratyphoid C (S. hirschfeldii)*.
- Salmonella organisms are gram-negative bacilli. They contain three types of antigens:
    - Somatic or cell wall lipopolysaccharide (O) antigen.
    - Flagellar (H) antigen.
    - Capsular or polysaccharide virulence (Vi) antigen located in the cell capsule.

Incidence

- In developing countries, the incidence is 500/100,000 (0.5%).

Epidemiology

- Adults and children of all ages and both sexes are equally susceptible to infection. Most cases occur in school-age children and young adults.
- Although acquired immunity provides some protection, re-infections have been documented. Typhoid fever may occur during all seasons.

- Major reservoirs for *Salmonella* are animals (poultry, pets), contaminated water, infected fruits and vegetables, and infected humans.
- *S. typhi* is resistant to drying and cooling, thus allowing bacteria to survive prolonged periods in dried sewage, water, food, and ice.
- *S. typhi* infects only humans.
- Infection is transmitted by ingestion of contaminated food, milk, water, or contact with an infected animal.
- Person-to-person spread occurs by the fecal-oral transmission. For a clinical disease to occur, 10^5–10^9 viable organisms must be ingested.
- Attack rates peak in the first year of life and are higher for children younger than 5 years of age.
- Outbreaks of disease may occur by contaminated water or ingestion of the contaminated eggs. The source of the domestically acquired typhoid is usually a person who is a chronic carrier of S. typhi.
- Incubation period for enteric fever is usually 7–14 days (range 3–30 days). It depends upon the size of the ingested inoculum and immune status of the host.

Pathogenesis

- Bacteria enter the body mostly by ingestion of contaminated food or water.
- After ingestion of *S. typhi*, the part of the inoculum that survive the acidity of the stomach enters the small intestine, where bacteria penetrate the mucosa and enter mononuclear phagocytes of ileal Peyer's patches and mesenteric lymph nodes.
- There is necrosis of the Peyer's patches, which causes sloughing of the overlying epithelium leading to the ulcers, which may bleed. These ulcers heal without scarring.
- If the inflammation is severe, these inflammatory lesions may erode the intestinal wall leading to the intestinal perforation.
- Infection spreads to the regional lymph nodes where multiplication takes place in the mononuclear cells.
- Via the intestinal lymphatics, the organisms not destroyed by the monocytes reach the liver, spleen, mesenteric lymph nodes, and bone marrow and proliferate there.
- At the end of the incubation period, they pass into the blood stream and produce bacteremia and its associated symptoms (enteric fever syndrome).
- A large number of the salmonella are produced by the local multiplication of the organisms in the wall of the gallbladder and they reach the intestine through bile.
- Prolonged fever and toxic symptoms are produced by a circulating endotoxin (a lipopolysaccharide component of the bacterial cell wall) and endotoxin-induced cytokine production by macrophages.
- Cell-mediated immunity has a very important role in protecting a person from typhoid fever. This immunity is decreased or impaired in critically ill patients and carriers.
- Carriers pass a large number of *S. typhi*. These bacilli do not enter the gut epithelium of the host.

Clinical findings

- The incubation period of typhoid fever is usually 7–14 days (depends on the infecting dose and ranges between 3 and 30 days).
- The presentation of typhoid fever may also differ according to age.
- In infants, it may cause mild gastroenteritis or severe sepsis. Vomiting, diarrhea and abdominal distension are common. Fever is continuous and high-grade and may cause febrile fits. There may be anorexia, weight loss, jaundice and hepatosplenomegaly.
- The older child presents with high-grade continuous fever. Headache is common with malaise, anorexia, lethargy, myalgia, abdominal pain and tenderness. The typical patient has an extremely toxic look with long drawn face and furred tongue (central). The child is pale looking and has lost weight. He may have cough with scattered rhonchi or crepitations giving suspicion of pneumonia. Rarely jaundice may be present from septicemia involving liver. The paradoxical relationship of high temperature and low pulse rate may not be seen in children.
- A maculopapular 1–5 mm rash (rose spots) are common (25% of the patients) on the upper abdomen and lower chest. They appear on 7th–10th day as crops (10–15 lesions) and last for 2–3 days. Rose spots are slightly raised lesions and blanch on pressure. These are formed by bacterial emboli. Culture of the material from the lesions may show *Salmonella* in 60% of the cases. When rose spots heal, a slight brownish discoloration of the skin remains.
- The soft spleen may be palpable during the second week. There is usually abdominal tenderness with mild distension unless some complication occurs.
- There may be delirious muttering with stupor. The clinical course usually lasts for about 2–4 weeks with gradual recovery.
- Relapse may occur in 7–10% of cases.
- Persons who excrete the organisms for longer than 1 year are called chronic carriers. Gallbladder disease predisposes to chronic carrier stage.
- In about 10% of the patients with Salmonella bacteremia, focal infections may occur. These include osteomyelitis, meningitis, pneumonia, pyelonephritis, endocarditis, and arthritis.

Diagnosis

- Despite these innovations, the mainstay of diagnosis of typhoid remains clinical in much of the developing world,

Isolation of causative organism (culture)

- Diagnosis is confirmed by the culture showing *Salmonella strain*.
    - Blood culture (positive early during the first 2 weeks of illness in 40–60% cases).
    - Culture of bone marrow.
    - Urine and stool culture (late).
- Stool culture may be positive during the incubation period, but bone marrow is mostly positive during the later stages of the enteric fever. Bone marrow culture is the most sensitive procedure (positive in 85–90%) to recover the *S. typhi* (collection of the specimens is difficult and relatively invasive).

Serological tests

Widal test

- This procedure measures the antibody response to somatic and flagellar antigens of *Salmonella*.
- "O" antibody titers of greater than 1:160 are suggestive. Demonstration of rising titer over 7–10 days against "O" antibody is also helpful in diagnosis.
- "H" antibody (flagellar antigen) signifies previous infections or immunization and is difficult to interpret in endemic areas.
- Widal's test may give false-positive or false-negative results, so it is not a reliable test to diagnose the enteric fever. False-positive results are often obtained in endemic areas and false-negative results occur in some cases of bacteriologically proven typhoid fever.

Polymerase Chain Reaction (PCR)

- PCR is used to amplify the specific genes of *S. typhi* in the blood.
- It gives the results within a few hours and is more specific and sensitive than blood culture.

Supportive tests

- CBC:
    - Leucopenia may be present in spite of the high-grade fever.
    - There may be a wide range in counts; in younger children leukocytosis is common and may reach 20,000–25,000 cells/μL.
    - There may be a normochromic normocytic anemia. It is due to bone marrow suppression or intestinal blood loss.
    - Thrombocytopenia may be present.
- Liver function test may be deranged with involvement of the liver.

Table 10.10: Typical signs and symptoms of typhoid fever.

Disease period	*Signs and symptoms*	*Pathology*
First week	Fever and chills gradually increasing and persisting (95% cases), headache, abdominal tenderness.	Bacteremia.
Second week	Rash, abdominal pain, diarrhea or constipation, delirium, prostration, rose spots, splenomegaly, and hepatomegaly.	Mononuclear cell vasculitis of skin, hyperplasia of ileal Peyer's patches, typhoid nodules (focal collection of mononuclear leukocytes) in spleen and liver.
Third week	Complications of intestinal bleeding and perforation, shock. Melena, ileus, rigid abdomen, coma.	Ulcerations over Peyer's patches, perforation with peritonitis.
Fourth week and later	Restoration of symptoms, relapse, weight loss, reappearance of acute disease, cachexia.	Cholecystitis, chronic fecal carriage of bacteria.

Differential diagnosis

- Gastroenteritis if abdominal symptoms are present
- Bronchopneumonia if the respiratory symptoms are present
- Sepsis
- Malaria
- Tuberculosis
- Acute hepatitis
- Amebic liver abscess
- Shigellosis
- Miliary tuberculosis
- Brucellosis
- Leptospirosis
- Bacterial endocarditis
- Infectious mononucleosis
- Malignancies such as leukemia or lymphoma

Complications

- Intestinal perforation (0.5–3.0%). Perforation usually occurs in the distal ileum. There is marked abdominal pain, tenderness, and vomiting. Signs of peritonitis are present. Bowel sounds are diminished and the abdominal radiograph usually reveals free air. Perforation most often occurs unexpectedly after a few days of treatment when a patient has started to improve.
- Intestinal hemorrhage (1–10%). It is suspected if there is a drop in temperature and blood pressure and an increase in the pulse rate.

- Toxic encephalopathy. There may be increased intracranial pressure, cerebral thrombosis, acute cerebral ataxia, chorea, psychosis, aphasia, deafness, peripheral and optic neuritis, or transverse myelitis.
- Acute cholecystitis or hepatitis.
- Pneumonia due to superinfection with organisms other than *Salmonella* is common.
- Pyelonephritis
- Meningitis
- Osteomyelitis
- Septic arthritis (in children with hemoglobinopathies)
- Sepsis
- Toxic myocarditis (arrhythmias, sino-atrial block, ST-T changes on EEG, or cardiogenic shock)
- Fatal bone marrow suppression
- Most of the complications occur after the 2nd week of the disease

Management

Specific

- Choice of the antibiotic should be according to the culture reports and antibiotic resistance.
    - ○ Chloramphenicol 50–75 mg/kg/24 hours PO or 75 mg/kg/24 hours IV in 4 divided doses (maximum 3 g/day) for 14–21 days. IV treatment is given until the patient is able to take oral medication. Chloramphenicol is very effective to sterilize the blood but the relapse rates are high. Chloramphenicol neither prevents nor effectively treats the chronic carrier state.
    - ○ Amoxicillin, 100 mg/kg/24 hours PO in 3 divided doses for 14 days.
    - ○ Fluoroquinolones (e.g. ofloxacin or ciprofloxacin) are effective. Ciprofloxacin is given 15–20 mg/kg/24 hours PO for 10–14 days
    - ○ Ceftriaxone 60 mg/kg/day in 2 doses IV for 14 days
    - ○ Azithromycin 10–20 mg/kg/day orally for 7 days
    - ○ Cefotaxime 80 mg/kg/day IV divided in three doses for 14 days
    - ○ Cefixime 20 mg/kg/day orally for 7–14 days
- After effective treatment, most children become afebrile within 7 days. Total duration of therapy should be 10–14 days.

Table 10.11: Treatment of typhoid fever.

Susceptibility	Antibiotic	Daily Dose (mg/kg/day)	Days	Antibiotic	Daily Dose (mg/kg/day)	Days
Uncomplicated typhoid fever						
Fully sensitive	Chloramphenicol	50–75	14–21	Fluoroquinolone, e.g. ofloxacin or ciprofloxacin	15	5–7*
	Amoxicillin	75–10	14			
Multidrug-resistant	Fluoroquinolone	15	5–7	Azithromycin	8–10	7
	or					
	Cefixime	15–20	7–14	Cefixime	15–20	7–14
Quinolone-resistant*	Azithromycin	8–10	7	Cefixime	20	7–14
	or					
	Ceftriaxone	75	10–14			
Severe typhoid fever						
Fully sensitive	Fluoroquinolone, e.g. ofloxacin	15	10–14	Chloramphenicol	100	14–21
				Amoxicillin	100	
Multidrug-resistant	Fluoroquinolone	15	10–14	Ceftriaxone	60	10–14
				or		
				Cefotaxime	80	10–14
Quinolone-resistant	Ceftriaxone	60	10–14	Azithromycin	10–20	7
	Cefotaxime	80	10–14	Fluoroquinolone	20	7–14

Supportive

- Corticosteroids are given in individuals with severe toxemia or prolonged symptoms. A short course of dexamethasone improves the survival rate of patients presented with shock or coma. Initial dose of dexamethasone is 3 mg/kg, followed by 1 mg/kg every 6 hours for 48 hours.
- Blood transfusion is needed in a patient with anemia or severe intestinal bleeding.
- Adequate nutrition, hydration, and electrolyte balance is essential.
- If there is intestinal perforation, surgical intervention is required along with good cover of broad-spectrum antibiotics.
- If there is thrombocytopenia, platelet transfusion is needed to avoid bleeding.

Prevention

- Hand-washing, improved personal hygiene and sanitary habits are very important preventing measures.
- Protective health measures (provision of clean water, adequate sewage disposal, and control of flies) are also important.
- Adequate temperatures for cooking. Eggs should be thoroughly cooked and never eaten raw. Avoid preserving food at warm temperatures and reheating food.
- Passive immunization with vaccination.

Prognosis

- Mortality rate is higher than 10% and is mainly due to delay in diagnosis or treatment. Infants and children with some severe underlying illness are at greater risk.
- Enteric fever with complications is associated with high morbidity and mortality.
- Relapse may occur in 4–8% of the patients who have not got the treatment. Relapse may also occur in the treated patient about 2 weeks after stopping the antibiotics. Signs and symptoms of relapse are usually mild and of shorter duration.
- Children have a low risk to become a carrier. As a whole, 1–5% of the enteric patients become carrier. Chronic carriers are at increased risk to get biliary tract disease.

POLIOMYELITIS

CASE

A 4-year-old boy presents with ***fever*** and ***asymmetrical flaccid paralysis*** of lower limb.

- Poliomyelitis is an acute viral infection in human beings.
- It may produce a mild illness or a rapidly progressive illness leading to encephalitis, paralysis, and death.
- Poliovirus infection is sub-clinical (asymptomatic) in 90–95% of cases.
- It causes non-specific febrile illness (minor illness with low-grade fever and sore throat) in about 5% of cases.
- Aseptic meningitis or paralysis occurs in 1–5% of cases.
- Rapid onset of asymmetric acute flaccid paralysis with areflexia of the involved limb occurs in 0.1–2% of infections, and residual paralytic disease involving the motor neurons (paralytic poliomyelitis) occurs in approximately 1 per 250 infections.
- Rarely, severe poliovirus infection can occur after oral poliovirus vaccination (due to reversion of the vaccine virus). Its incidence varies with age of the patient and virus type and is 1 in 6 million doses of OPV.
- Adults who got paralytic poliomyelitis in childhood may develop 30 to 40 years later the post-polio syndrome (characterized by muscle pain, exacerbation of weakness, and/or new paralysis or weakness).

Etiology

- The etiologic factor is an RNA entero-virus called poliovirus.
- There are three serotypes (I, II, III) responsible for the disease.

Epidemiology

- Humans are the only natural reservoir for poliovirus.
- Transmission is mainly by fecal-oral route and possibly respiratory route.
- Perinatal transmission from mother to newborn infant can occur.
- Poliovirus has been isolated from feces for longer than 2 weeks before paralysis to several weeks after the onset of symptoms.
- Infection is more common in infants and young children, and occurs at an earlier age in living conditions of poor hygiene.
- Communicability is greatest shortly before and after onset of clinical illness when the virus is present in the throat and excreted in high concentration in the feces.
- The virus persists in the throat for about 1 week after onset of illness and is excreted in the feces for several weeks and occasionally for months.
- Patients are potentially contagious as long as fecal excretion persists.
- After OPV vaccination, virus persists in the throat for 1–2 weeks. It is excreted in the feces for several weeks (in rare cases for more than 2 months). Immunodeficient patients may excrete virus for prolonged periods.
- In endemic areas, older children are immune because of prior inapparent infections.
- Infants get immunity transplacentally from their mothers.
- Transplacental immunity disappears at a variable rate during the first 4–6 months of life.

- Active immunity after natural infection may be lifelong but it only protects against the infecting serotype. Infections with other serotypes are possible.

Incubation period

- For the onset of paralysis in paralytic poliomyelitis, the incubation period is usually 8–12 days, but occasionally it is as short as 5 days.

Pathogenesis

- Virus enters the body by the oropharyngeal route and multiplies in the alimentary tract.
- Infection involves the regional lymph nodes within one day.
- Viremia of short duration is followed by the appearance of the type specific antibodies in the blood and alimentary tract.
- If virus particles are neutralized then no clinical illness occurs.
- If antibodies fail to neutralize then virus may proliferate and become invasive. It causes invasion and destruction of motor neurons (anterior horn cells) in the CNS and spinal cord. The virus multiplies in the neurons and may lead to damage or destruction.
- Clinical picture depends upon the neuronal involvement.
- Spinal cord (anterior horn cells chiefly)
- Medulla (cranial nerve nuclei)
- Cerebellum (gray cell nuclei and vermis)
- Cerebral cortex (motor cortex)

Immune response

- Passive antibodies from mother transferred through placenta in the infant persist up to 6 months of age.
- After natural infection, active immunity lasts for life.
- Due to the replication of the virus in the intestinal tract and lymphatic tissues, neutralizing antibodies against poliovirus form within several days after exposure to the virus (often before the appearance of signs and symptoms of the disease).
- One most important defense against poliovirus infection is by the production of local mucosal immunity by secretory Immunoglobulin (IgA).

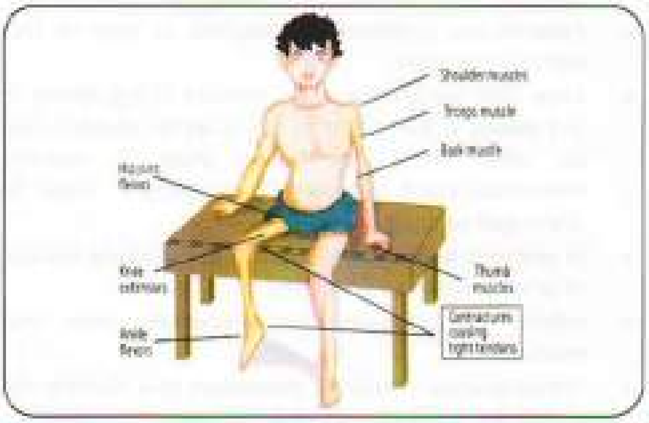


Figure 10.2: Muscles commonly affected by poliomyelitis.

Clinical findings

When a susceptible person comes in contact with poliovirus, one of the following responses may occur:

1. Asymptomatic (inapparent) infection
2. Abortive poliomyelitis
3. Non-paralytic poliomyelitis
4. Paralytic poliomyelitis

Asymptomatic poliomyelitis

- 95% of the infected persons are asymptomatic.

Abortive poliomyelitis: (non-specific febrile illness)

- There is a brief febrile illness with one or more of the symptoms like malaise, anorexia, nausea, vomiting, headache, sore throat, constipation, and abdominal pain.
- Usually fever does not rise above 103°F (39.5°C).

Non-paralytic poliomyelitis: (aseptic meningitis)

- The poliovirus has entered the nervous system without destroying the neurons.
- The initial symptoms (called minor illness) are fever, myalgia, sore throat, and headache for 2–6 days.
- After some days, signs of aseptic meningitis appear (recurrent fever, headache, stiff neck, spinal rigidity, and nausea).
- Transient bladder paralysis and constipation may occur.
- Mild cases resolve completely.
- This second phase is called central nervous system or major illness. There is a short symptom free period between minor and major illness.
- Nuchal and spinal rigidity is a necessity for the diagnosis of non-paralytic poliomyelitis. This can be tested by "Kiss-the-knee" and "tripod" signs. Neck stiffness can be elicited by Kernig and Brudzinski signs.
- Superficial reflexes are usually depressed 12–24 hours before the onset of paralysis. These reflexes are cremasteric, abdominal, spinal and gluteal.
- Deep tendon reflexes are depressed or exaggerated 8–24 hours after depression of superficial reflexes and indicate impending paralysis. Tendon reflexes are absent after the onset of paralysis. No sensory deficit occurs objectively.

Paralytic poliomyelitis

- In addition to signs and symptoms of non-paralytic poliomyelitis, symptoms of weakness of one or more muscle groups occur, either skeletal or cranial.
- There is deeper brain involvement with signs and symptoms of pain, spasticity, hypertonia, respiratory and cardiac arrhythmias, blood pressure and vasomotor changes, and bladder and bowel dysfunction.
- Paralysis is usually asymmetric.
- Paralysis is usually complete by the time temperature normalizes.

- Weakness usually persists. Some improvement of paralysis occurs within 6 months. Remaining weakness improves with physiotherapy.

Clinical classification of paralytic poliomyelitis

- Clinical paralysis generally extends during the first week reaching its limits as the fever subsides.
- Paralysis is characteristically patchy and asymmetric and various forms are recognized.

Spinal form

- There is weakness of some of the muscles of the neck, abdomen, trunk, diaphragm and extremities.
- Cervical and thoracic spinal cord segments are mainly affected.
- There is respiratory insufficiency characterized by tightness, weakness, or paralysis of respiratory muscles (mainly the diaphragm and intercostal muscles).

Bulbar form

- Pure bulbar poliomyelitis refers to motor cranial nerve nuclei with or without involvement of vital centres.
- Involvement of ninth, tenth, and twelfth cranial nerves leads to the paralysis of pharynx, larynx and tongue (swallowing, speech, and cardio-respiratory function). Bulbar form accounts for most deaths.
- The clinical findings of bulbar poliomyelitis are:
  - Nasal twang to the voice or cry
  - Inability to swallow and accumulation of saliva in the pharynx
  - Nasal regurgitation
  - Lack of effective coughing
  - Deviation of the uvula or the tongue
  - Paralysis of the cords resulting in hoarseness or aphonia
  - Immobilization leads to atrophy of non-paralytic muscles and decubitus ulcers

Bulbospinal form

- There is combined involvement of spinal and bulbar regions.

Encephalitic form

- It is relatively uncommon form. There is irritability disorientation, drowsiness and coarse tremors.

Diagnosis

- Diagnosis of poliomyelitis is mainly clinical.
- Poliomyelitis should be considered in any unimmunized or incompletely immunized child with paralytic disease.
- In patients with signs of meningeal irritation, the CSF has up to several hundred leukocytes, which are mostly lymphocytes. Glucose level is normal and protein level is mildly elevated.
- Poliovirus may be isolated from CSF for 3–5 days after meningitis is apparent or from throat and stool for several weeks after infection.
- The **diagnostic test of choice** for confirming poliovirus disease is viral culture of stool specimens. Two or more stool specimens for poliovirus isolation are obtained at least 24 hours apart from patients with suspected paralytic poliomyelitis as early as possible in the course of the illness (ideally within 14 days of onset of symptoms). Fecal material has high yield of virus, but virus can also be recovered from rectal swabs.

Differential diagnosis

Poliomyelitis should be considered in the differential diagnosis of any case of paralysis.

- Aseptic meningitis
- Guillain-Barre' syndrome (variable sensory loss, symmetric loss of function, pyramidal tract signs, minimal pleocytosis, high protein concentration in spinal fluid)
- Polyneuritis (sensory loss)
- Pseudo-paralysis due to bone or joint problems (e.g. trauma, infection)
- Transverse myelitis
- Traumatic neuritis
- Botulism
- Tick paralysis

Complications and sequelae

- Acute and permanent effects of paralysis
- Respiratory, pharyngeal, bladder, and bowel malfunction
- Melena due to single or multiple superficial intestinal erosions
- Acute gastric dilatation
- Mild hypertension (due to lesions of the vaso-regulatory centers in the medulla and underventilation)
- Hypercalcemia, nephrocalcinosis, and vascular lesions due to prolonged immobilization.
- Deaths are mainly due to complications as a result of respiratory dysfunction.

Management

- Therapy is mainly supportive.
- In abortive form, analgesics, sedatives, proper diet, and bed rest is all that is needed. Patient can be treated at home.
- Hospitalization is necessary for patients with paralytic poliomyelitis.
- Look carefully for progression of weakness (particularly of respiratory muscles).
- In addition to close observation for respiratory insufficiency, blood pressure should be taken at least twice daily. Impaired ventilation must be assessed early. Anxiety, restlessness, and fatigue are signs for early respiratory support.

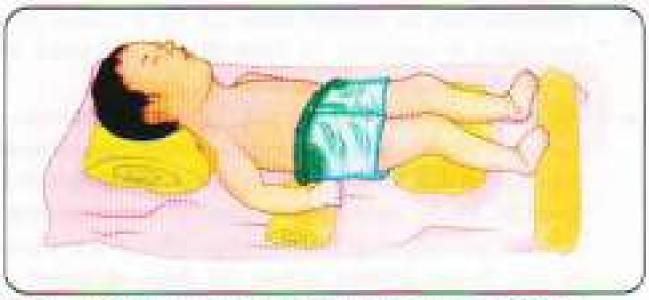


Figure 10.3: Neutral position with the elpof sand bags..

- Strict bed rest, and a neutral position are very important. In making the neutral position of the patient, feet should be at right angle, knees slightly flexed, and hips and spine should be straight. Neutral position can be made with the help of sand bags.
- Minimal handling of the affected parts.
- No intramuscular injection should be given.
- Analgesics and mild sedation for relief of pain and restlessness. Analgesics are more effective when given with application of hot packs for 15–30 minutes after every 2–4 hours. Hot tub bath may be appropriate.
- Maintenance of nutrition and hydration.
- Avoidance of constipation and bladder care.
- Keep airway patent by suction and watch for any respiratory distress. This is especially important in case of bulbar poliomyelitis. To avoid aspiration, head should be low, with prone position, and face to one side.
- After acute stage is over, physiotherapy should be started.
- Some children may require corrective splints or braces. Surgery is rarely required.

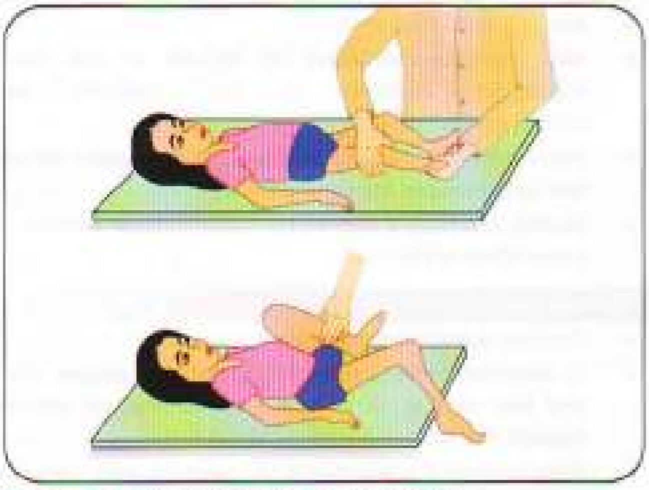


Figure 10.4: Physiotherapy in poliomyelitis.

Prognosis

- The mortality rate in paralytic polio varies from 5–10% and permanent paralysis occurs in 15% of the cases.
- Mild paralysis may occur in up to 30% of cases.
- The more extensive the paralysis in the first 10 days of illness, the more severe is the ultimate disability.

Prevention

- Polio vaccine affords a high degree of protection against poliomyelitis when adequately immunized against all 3 types.
- Newborn infants whom mother's sera contain antibodies to all 3 serotypes are passively immune for first few months.
- Both inactivated (Salk, IPV) and attenuated (Sabin, OPV) vaccines produce satisfactory immunity. Live attenuated vaccines should not be administered to immuno-compromised children.
- In three-dose series, OPV results in sustained, probably lifelong immunity. Vaccination with two or more doses of OPV induces excellent intestinal immunity against poliovirus re-infection (explains its effectiveness in controlling wild-virus circulation).
- The only adverse reaction to poliomyelitis vaccination is Vaccine-Associated Paralytic Poliomyelitis (VAPP) due to OPV.

DIPHTHERIA

CASE

A 6-year-old child presents with high grade ***fever*** and ***severe respiratory distress***. On examination, there is ***swelling of neck***. There is a greyish yellow ***membrane over throat***.

Etiology

- Diphtheria is an acute infectious disease of the upper respiratory tract or skin caused by an exotoxin producing organism, *Corynebacterium diphtheriae*.
- *Corynebacterium diphtheriae* is a gram-positive club shaped bacillus with a beaded appearance, which grows well on tellurite agar or Loffler's medium.
- Three strains are recognized according to their degree of virulence: *Gravis, Mitis and Intermedius*. In fact, the *Intermedius* biotype is most frequently toxigenic (98.9%).

Epidemiology

- *C. diphtheriae* is an exclusive inhabitant of human mucous membranes and skin.
- Diphtheria is a highly contagious infection that spreads most easily under socioeconomic conditions in which there is poor personal hygiene, crowding, and limited access to medical care.
- The primary route of transmission has been by aerosol or transfer of respiratory secretions from an infected individual. Skin infection may occur in many different forms, such as purulent punched out ulcers, impetiginous lesions, and wound infections.
- Immunization status influences susceptibility to infection and severity of disease in the individual patient. When disease does occur in immunized or

partially immunized patients, mortality (1.3%) is 10-fold lower than in non-immunized individuals (13.4%).

Pathogenesis

- Diphtheria is spread by personal contact with a patient or a healthy carrier (asymptomatic respiratory carriers are important in transmission).
- The bacilli gain entry to the pharynx and may spread to larynx or nose.
- The bacteria remain localized to the mucosal surface and multiply rapidly producing exotoxin.
- Diphtheria toxin is an extremely potent inhibitor of protein synthesis. Locally it produces hyperemia and edema and destruction of superficial epithelium resulting in the formation of pseudomembrane (commonly present over the tonsils, pharynx, or larynx), which consists of necrotic tissue, fibrin, white cells and bacteria. The membrane is adherent to the underlying surface. Any attempt to remove the membrane exposes and tears the capillaries, resulting in bleeding into the larynx and trachea causing respiratory embarrassment. The diphtheria bacilli within the membrane continue to produce toxin, which is absorbed and may result in toxic injury.
- The effect of the exotoxin is mainly on the myocardium, peripheral nerves, kidneys, liver and adrenals.

Clinical findings

- The incubation period is 2 to 4 days.
- The illness may be so mild to be overlooked in partially immune children or it may be fulminating leading to death in a short time.
- Most commonly it is of insidious onset with mild to moderate fever, malaise and headache but sore throat is not conspicuous.

Pharyngeal diphtheria

- Severe systemic disease and mortality occur most frequently in patients with pharyngeal infection and are largely attributable to the exotoxin released by the bacteria at the site of localized infection.
- Early manifestations of diphtheritic pharyngitis are mild sore throat, moderate fever, and malaise.
- The grayish membrane may be unilateral or bilateral on tonsils, uvula or soft palate which bleeds on attempted removal.
- Difficulty in breathing and stridor may occur even without laryngeal involvement.
- There may be difficulty in swallowing.
- The patient usually has a dull sensorium, prostration, and is toxic in spite of no or mild fever. Pulse is more rapid than suspected by the grade of the fever.
- Palatal paralysis may occur resulting in nasal regurgitation of food and nasal quality to the voice.
- The cervical lymph nodes may become enlarged and together with edema of subcutaneous tissue of the neck produce the characteristic brawny edema of the neck ("bull neck" appearance).

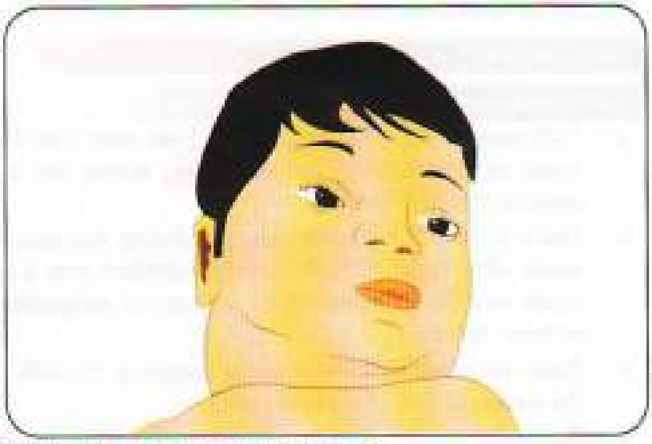


Figure 10.5: Bull neck in diphtheria.

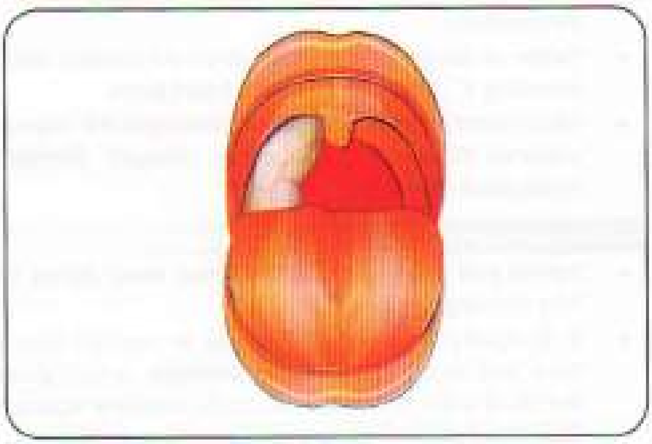


Figure 10.6: Pharyngeal diphtheria.

Laryngeal diphtheria

- Patient with laryngeal involvement presents with hoarseness of voice, brassy cough, increasing stridor and respiratory obstruction resulting in subcostal, suprasternal and infrasternal recessions.
- The child is extremely anxious, restless and may become cyanosed and die of suffocation unless airway is maintained by tracheostomy or intubation.

Nasal diphtheria

- Occasionally diphtheria affects nasal passages only.
- It may produce a mild disease and results in characteristic serosanguineous nasal discharge and excoriation of the upper lip. It may cause unilateral or bilateral purulent bloodstained discharge simulating a foreign body in the nostril. A foul odour may be noticed and there may be a white membrane on the nasal septum.

Other forms

- Cutaneous, vaginal, and wound diphtheria are characterized by ulcerative lesions with membrane formation.

- In cutaneous diphtheria, infection is non-progressive. It is characterized by a superficial, non-healing ulcer with a gray-brown membrane.

Complications

Toxic cardiomyopathy: (In 10–25 % of cases)

- Toxic myocarditis may occur from 2–40 days after the onset of pharyngitis (most commonly during the 2–6 week of infection).
- There is circulatory failure usually during the second week with rapid, thready pulse; indistinct and poor heart sounds, hepatomegaly, pulmonary congestion, or heart failure.
- Toxic myocarditis is the cause of death in 50–60% of the cases.
- Tachycardia out of the proportion to fever is the evidence that there is cardiac toxicity or autonomic dysfunction.
- Single or progressive cardiac dysrhythmiascan occur, including 1st, 2nd, and 3rd degree heart block.
- Electrocardiography will reveal prolonged PR interval, elevated ST segment or T wave changes. Complete heart block may occur.

Toxic neuropathy: (Occurs in 10–20% cases)

- Palatal and pharyngeal paralysis may occur during the first or second week.
- It is usually transient and results in regurgitation of food and nasal voice. Ocular paralysis occurs during the third week resulting in diplopia, paralytic squint or blurring of vision.
- Peripheral neuritis may occur involving the motor nerves between fifth to seventh weeks. It may result in paralysis of the limbs with loss of deep tendon reflexes. Generalized paralysis may occur. But it is always transient if patient survives.
- CSF findings may be same as GB syndrome.

Bronchopneumonia

- Secondary infections, especially streptococcal bronchopneumonia are a common cause of death in cases of laryngeal diphtheria.

Miscellaneous

- Complications may occur involving the liver and kidneys resulting in hepatitis and nephritis.
- Renal changes resulting in albuminuria, casts and diminished urine output, but does not lead to permanent loss of renal function.
- Adrenal hemorrhage and gastritis may occur.

Diagnosis

- It is suspected on clinical grounds in areas where diphtheria is still common.
- The bacteriological confirmation depends on the isolation of the organism and determining its virulence.

Direct smear

- In order to demonstrate the organism, the swabs should be taken from the suspected lesions preferably after removing some of the membrane.
- Direct smears are unreliable.
- Since co-infection with staphylococci and streptococci can occur, the presence of these organisms does not rule out diphtheria.

Culture

- The isolation of the organism on culture confirms the clinical suspicion but while waiting for the culture report, patient should be put on treatment.
- Material is obtained from nose, throat, or skin lesions and cultured on Loffler's and tellurite agar.
- Sixteen to 48 hours are needed to identify the organisms.
- Cultures may be negative in children who have taken antibiotics.

Complete blood count

- The white blood cell count is usually normal, but there may be a slight leukocytosis.
- RBC count may show the evidence of rapid destruction of erythrocytes.
- Thrombocytopenia is due to peripheral destruction of thrombocytes.

Differential diagnosis

Pharyngeal diphtheria should be differen[illegible]

following

- Acute streptococcal pharyngitis:
  - It causes pain on swallowing
  - Fever is high grade
  - Membrane is non-adherent
- Thrush:
  - Whitish spots or membrane on tongue and also on buccal mucosa
  - Minimal constitutional upset
- Herpetic infection:
  - Shallow ulcers on buccal, tonsil and gingival mucosa are present.
  - These are painful.
  - There is foul breath odour.
- Agranulocytosis:
  - It has similar but whitish membrane.
  - Diagnosis is confirmed by low blood count.
- Infectious mononucleosis:
  - It is associated with generalized lymphadenopathy and splenomegaly.
  - Atypical lymphocytes in the blood.
  - Paul Bunnel test is positive.

Laryngeal diphtheria should be [illegible]

following

- Acute epiglottitis

  - Child is extremely toxic
  - Having high-grade fever
  - On examination epiglottis is "cherry-red" in color
- Laryngo-tracheo-bronchitis
  - Cough is more prominent with stridor
  - Child is non-toxic
  - And has low grade fever

Nasal diphtheria has to be differentiated from

- Foreign body in the nostril
- Purulent sinusitis

Neuropathy due to diphtheria

- Neuropathy may be a manifestation of Guillain-Barre' syndrome, poliomyelitis, or acute poisoning.

Management

- The goal of therapy in a patient with presumed or documented diphtheria are:
  - Neutralization of free toxin
  - Elimination of further toxin production
  - Control of the local infection
  - Support during the course of the systemic intoxication phase
  - Prevention of transmission
- The mainstay of the treatment, therefore, is:
  - Diphtheria antitoxin
  - Antibiotics
  - Supportive intervention directed at complications such as respiratory compromise, congestive heart failure, cardiac arrhythmias, neuropathies, renal failure, and bleeding diathesis
  - Strict isolation
- Treatment should be started on clinical suspicion of the disease while awaiting laboratory confirmation.
- Children suffering from diphtheria should be admitted in the hospital and treated vigorously.

Specific measures

Anti-toxin

- Prompt administration (within 48 hours) of diphtheria antitoxin is essential. Because it neutralizes only free toxin, antitoxin efficacy diminishes with passing time after the onset of mucocutaneous symptoms.
- A single dose is given intravenously to avoid the risk of sensitization from repeated doses of horse serum.
- Patient's sensitivity to horse serum should always be tested before giving antitoxin and always have injection adrenaline at hand for allergic reactions.
- The dose of antitoxin is based upon the site and extent of local infection and the severity and duration of symptoms at the time of presentation.
- Patients with cutaneous infection generally do not experience toxicity, but a low dose of antitoxin (20,000 units) is given.
- A dose of 20,000 to 40,000 units of antitoxin is recommended for patients with limited pharyngeal disease of 2 days' or less duration.
- Patients with more extensive nasopharyngeal involvement, especially of greater than 3 days' duration and associated with bull neck and other complications, require 80,000 to 100,000 units of antitoxin.

Antibiotics

- Treatment with penicillin or erythromycin should be followed by repeat culture to document elimination of the organism because there may be resistance to any antibiotic especially to erythromycin.
- Erythromycin is given orally or IV (40–50 mg/kg/day).
- Benzyl penicillin may also be given.
- Antibiotic therapy is not a substitute for antitoxin therapy.

Supportive measures

- Droplet precautions are instituted for patients with pharyngeal diphtheria.
- For patients with cutaneous diphtheria, contact precautions are observed.
- Bed rest for 2–3 weeks especially if myocarditis is present which should be looked for daily. It is extremely important during the acute stage, as myocarditis may get worse with activity.
- Serial ECGs should be done (2–3 times a week) for 4–6 weeks to detect myocarditis.
- Maintain fluid and electrolyte balance.
- Tracheostomy/intubation in laryngeal diphtheria should be done before the child exhausts.
- Feeding: nasogastric tube feeding is done as palatal and pharyngeal paralysis may result in aspiration and choking.
- Ventilation: respiratory paralysis may occur after 6–8 weeks of pharyngitis and assisted ventilation is required till the patient resumes spontaneous respiration.
- Patient recovering from diphtheria should be immunized against the disease as half the patients do not develop immunity and are susceptible to re-infection.

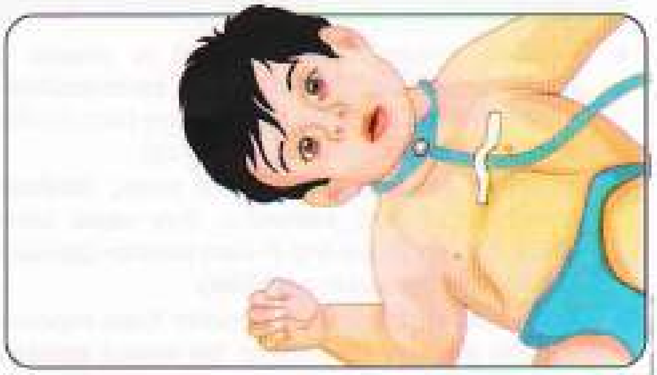


Figure 10.7: Tracheostomy due to diphtheria

Treatment of carriers

- All carriers should be treated.
- Erythromycin (40 mg/kg/day orally, or Benzathine Penicillin G (6 Lac–12 Lac units IM) should be given.
- All carriers must remain at home. Before the completion of the isolation, carriers must have 3 negative cultures of nose and throat (taken 24 hours apart) after the cessation of antibiotic therapy.

Prevention

- All suspected diphtheria cases should be reported to local and state health departments.

Immunization

- Immunization with DPT (diphtheria toxoid combined with pertussis and tetanus toxoid) is part of EPI program and should be used for infants and children.

Care of exposed susceptible (contacts)

- Children exposed to diphtheria should be examined. Their nose and throat cultures should be obtained. If signs and symptoms of diphtheria are present, treatment of diphtheria should be started.

Prognosis

- Prognosis is favorable if anti-toxin is given early. Mortality rate is less than 5% if antitoxin is used in time.
- Death may be due to airway obstruction by the diphtheritic pseudomembrane or severe myocarditis.

PERTUSSIS (WHOOPING COUGH)

CASE

A 3-month-old infant has a six days history of a mild cough. There are thick nasal secretions, poor feeding but no fever. In the last 10 hours she has developed ***spasmotic coughing*** with vomiting (***posttussive emesis***) and ***cyanosis*** (apnea). She is ***losing weight***. There are no examination findings between coughing spells. The chest radiograph shows ***peribronchial thickening***. Complete blood count reveals 30,000 white blood cells with 95% lymphocytes (***lymphocytosis***).

- Pertussis (means intense cough) is caused by *Bordetella pertussis* (a gram-negative cocco-bacillus) is a highly infectious disease of respiratory tract affecting susceptible children under 2 years of age.
- *Bordetella parapertussis*(in 5% of cases), *Bordetella bronchiseptica*, and *adenovirus* may cause similar illness, but less severe and of short duration (pertussis-like illness or pertusside syndrome).
- There is no cross immunity between these organisms and this probably accounts for the second attacks of whooping cough.

Epidemiology

- Pertussis is highly contagious.
- Attack rates are almost 100% in susceptible individuals.
- Humans are the only host of the *B. pertussis*.
- Transmission is by droplets during severe cough.
- The incubation period is between 3–12 days (mean 6 days).
- The infectivity is during the first four weeks of illness. Patients are most contagious during the pre-paroxysmal stage.
- It occurs at all ages but is most common and most severe under 5 years of age and the mortality is highest in infants under one year of age. There is little seasonal variation.
- Immunization reduces the incidence and mortality rate of pertussis. Active immunity follows natural pertussis. Neither natural disease nor vaccination provides complete (life-long) immunity against reinfection. Reinfection may occur years later but is usually mild. Immunity following immunization decreases in 3–5 years and is undetectable after 12 years.
- Intra-family spread is common and children usually acquire the disease from symptomatic family contacts. In adults, the syndrome is atypical with severe cough but no whoop.
- Carriers of *B. pertussis* are found infrequently, but persons previously immunized have been shown during outbreaks of disease to excrete the organism in the absence of clinical symptoms or in the presence of mild or atypical illness.

Pathology

- *B. Pertussis*adheres to ciliated epithelial cells of the respiratory tract and multiplies there without invading the tissue.
- The bacteria produce an endotoxin, which causes tissue necrosis, but a major virulence factor is exotoxin Pertussis Toxin (PT). PT is the main cause of lymphocytosis observed in a case of pertussis.
- There is inflammation of the respiratory mucosa from the nasopharynx to the bronchioles, causing patchy necrosis of the superficial epithelium, which is covered by the tenacious mucopurulent exudate containing masses of bacteria.
- The lumen of the bronchioles may become obstructed either causing obstructive emphysema or atelectasis and bronchiectasis may occur.
- The peri-hilar infiltrates produce the "shaggy" heart border on chest X-ray that is characteristic of pertussis.
- Cerebral hemorrhage and fatty infiltration of the liver may occur.

Clinical findings

- Clinical manifestations depends on the:
    - Specific pathogen

  - Patient's age
  - Host's immunization status
- The younger the child, the more atypical the signs and symptoms of the disease.
- Infants less than 6 months of age may have apnea, cyanotic spells, and cough but no whoop.
- Three stages are recognized: catarrhal, paroxysmal and convalescent stage. Each stage lasting about 2 weeks but the duration may vary according to the severity of the illness.

Catarrhal stage: (prodromal or pre-paroxysmal [illegible] weeks)

- Symptoms are indistinguishable from those of a mild viral upper respiratory infection.
- There is coryza (clear or mucoid rhinorrhea) with sneezing, conjunctival redness, and lacrimation.
- There is low-grade fever, wheezing and mild cough.
- The diagnosis is difficult during this stage and the child is most infectious.

Paroxysmal stage: (2–4 weeks or longer)

- The episodes of coughing increase in an effort to expel the bronchial exudate.
- After a series of coughing during a single expiration, there is a sudden massive inspiratory effort, which produces the whoop (air is inhaled forcefully against a narrowed glottis). The paroxysm may last half a minute or more and towards the end the child's face becomes red or even blue, the eyes protrude and neck veins get engorged and the appearance is of being strangled.
- Posttussive exhaustion is common. Vomiting may occur following a bout of paroxysm and should raise the suspicion of pertussis.
- Infants usually do not produce a whoop but they tend to get choked and may become intensely cyanosed.
- Infants with potentially fatal pertussis may appear completely well between episodes.
- During this stage the child may lose weight as a result of exhausting recurrent episodes of cough, poor appetite and may become dehydrated.
- In spite of respiratory symptoms there are no abnormal physical signs in the chest except occasional rhonchi.

Convalescent stage: (1–2 weeks)

- During this stage episodes of cough become less frequent and less severe and paroxysm of whooping disappear.
- The child's appetite improves but cough may persist in some patients for several months until full recovery occur.
- Pertussis may occur in a mild form as persistent cough in children who are immunized against this disease.

Complications

- **Bronchopneumonia** (in 25% of cases) due to *B. pertussis* itself or from secondary bacterial infection (*H. influenzae, Pneumococcus, S. aureus*) is the most common complication. It is responsible for more than 90% of deaths in infants. It is characterized by abrupt deterioration during the paroxysmal stage, associated with high fever and a striking leukemoid reaction with a shift to predominantly polymorphonuclear leukocytes.
- **Atelectasis** (due to mucus plugs) and later bronchiectasis.
- **Interstitial and subcutaneous emphysema.**
- **Otits media** and **sinusitis** are usually due to pneumococcus.
- **Convulsions** (in 4% infants) and coma may occur. Convulsions are particularly common in young infants and may lead to temporary or permanent neurological defects. There may be tetanic seizures due to alkalosis induced by persistent vomiting.
- **Encephalitis** (in 1% infants) may follow attack of pertussis or immunization.
- Rarely **epistaxis, retinal and subconjunctival hemorrhage, intracerebral and subarachnoid hemorrhages**, and **rupture of the diaphragm**, may occur. This is due to increased intra-thoracic pressure and venous engorgement.
- **Rupture of the frenulum** may occur during the paroxysms.
- **Rectal prolapse** and **umbilical or inguinal hernia** may occur.
- **Reactivation of quiescent tuberculosis** may occur due to depression of the cell-mediated immunity. It is advisable to give prophylactic INH for 3 months in patients who have pertussis.
- **Malnutrition** may follow.
- **Apnea** and **sudden death** may occur during a severe paroxysm.
- The forceful bout of cough may rupture alveoli and produce **pneumo-mediastinum, pneumothorax**, or **interstitial or subcutaneous emphysema**.
- Recurrent vomiting can lead to **metabolic alkalosis** or malnutrition.

Diagnosis

- Clinical diagnosis is only obvious during the paroxysmal stage.
- There is little difficulty in making the clinical diagnosis of whooping cough in a patient who, after a period of coryzal symptoms develops paroxysmal coughing (especially of more than 14 days duration) with a terminal inspiratory whoop, or posttussive vomiting. There is only a pure or predominant complaint of cough, especially if these features are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales.

- In infants younger than 3 months of age, apnea or cyanosis may be a clue of the disease. No or slight fever may be present. Temperature greater than 101°F (38.3°C) suggests bacterial super-infection or another cause of respiratory tract infection.
- A history of incomplete vaccination or a history of contact with a pertussis patient helps.
- In the early stages the diagnosis can be confirmed by laboratory investigations.

Blood counts

- There is **leukocytosis**. Count varies between 15,000 to 100,000 cells/mm^3 with 70–80% lymphocytosis (absolute lymphocytosis) near the end of catarrhal stage and during the paroxysmal stage.
- In viral infections there are large atypical lymphocytes but in pertussis the lymphocytes are normal small cells of T-cell or B-cell origin. This type of lymphocytosis may not be present in young infants and partially vaccinated children. The blood picture may resemble lymphocytic leukemia (leukemoid reaction).
- Polymorphonuclear leukocytosis suggests a secondary bacterial complication. **Fluorescent antibody staining** of nasopharyngeal secretions may provide a rapid and specific diagnosis directly, if available.

Culture

- In the early stages diagnosis can be confirmed by swabs, which are cultured on Bordet-Gengou media at the bedside.
- A sterile cotton swab wrapped about a flexible copper wire is passed through the nares, and mucus is obtained from the posterior pharynx. B. pertussis is readily killed by desiccation, so the specimen should be quickly plated onto fresh medium. The cough-plate is inferior to nasopharyngeal swabs but may give positive cultures during the first two weeks of illness. During the early stages *B. pertussis* can be isolated from 90% of patients.
- By the third or fourth week the organism can be recovered in only 50% of cases, and in the convalescent stage it is unusual to obtain a positive culture.

X-ray chest

- It shows peri-hilar infiltrates, shaggy border of heart, atelectasis, or emphysema.
- It helps in excluding the complications e.g. atelectasis.

Differential diagnosis

- Bronchiolitis
- *Pneumonia due to chlamydia, bacteria, or* cytomegalovirus)
- Cystic fibrosis
- Tuberculosis
- Asthma
- Intra-thoracic lymphadenopathy compressing the trachea and bronchi
- Foreign body inhalation

Management

Specific measures

- Erythromycin 30–50 mg/kg/day in 3 divided doses (maximum 2 g/day) is given for a period of 14 days. Antibiotics may be given in order to make the patient non-infectious. Treatment for less than 14 days may result in bacteriologic relapse.
- Azithromycin (10 mg/kg/day once a day for 5 days) or clarithromycin (15 mg/kg/day divided into two doses for 7 days) are also equally effective.
- The most valuable part of antibiotic therapy is the prevention and treatment of secondary bacterial complications. The drug of choice is penicillin G, although it has no effect on the *Bordetella pertussis* itself.
- In severe cases, corticosteroids and salbutamol nebulization may be effective.

General measures

- Young infants, particularly those under 6 months of age, should be hospitalized.
- It is important to maintain an adequate hydration and nutrition. Frequent small feedings are recommended. Nasogastric tube feeding and parenteral fluids may be necessary in serious cases.
- Oxygen and gentle suction may be required to remove profuse, viscid secretions. The child's posture should be adjusted to allow him to get rid of his secretions.
- Sedation and cough mixtures play only a minor part.
- Avoid mist therapy.
- Convulsions are treated by injectable diazepam or oral phenobarbitone.
- Isolate the patient for the first 5 days of therapy.

Prevention

- There is lack of transplacental immunity, so infants are highly susceptible to the infection. Pertussis vaccine is given as part of DPT vaccine (see chapter on immunization).
- Erythromycin is effective in preventing the pertussis in exposed infants and children.
- Close contacts of less than 7 years of age who have completed four doses of DPT vaccine should receive a booster dose of DPT if 3 years have been passed since the last booster dose of DPT. They should also be given erythromycin.
- Close contacts of more than 7 years of age need no vaccination. They should receive erythromycin as prophylaxis for 10–14 days.

Prognosis

- Mortality rate is less than 1%.
- In infants of less than 5 months of age mortality rate may be up to 40%. So, in endemic or epidemic areas of

the disease, the vaccine may be given at the age of 2 weeks.
- Cause of death in most cases is pneumonia, other pulmonary complications, asphyxia, or encephalopathy.

TETANUS

CASE

A 10-day-old infant presents with fever, ***inability to suck*** and ***inability to open mouth***. On examination, umbilicus is septic. On touching, he developed ***convulsions***.

- It is an acute, spastic paralytic disease caused by *Clostridium tetani*, which is spore forming, anaerobic gram-positive bacillus.
- Spores are resistant to heat or boiling.
- The vegetative forms of *C. tetani* are heat or disinfectant susceptible.
- *C. tetani* spores may be found in house dust, and feces of animals. Spores can survive in soil for years. Spores usually enter the body through a deep punctured wound.
- In the newborn umbilicus is the usual source of infection.
- *C. tetani* is not a tissue-invasive organism (i.e. it remains at the wound site and causes illness due to the effects of tetanospasmin).

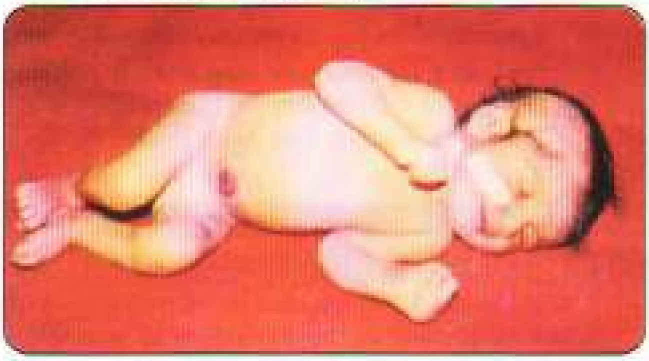


Figure 10.8: A baby with typical findings of tetanus.

Toxins

- It produces two exotoxins:
  - Tetanospasmin
  - Tetanolysin
- It is the tetanospasmin, which is neurotoxic while tetanolysin potentiate the effect of tetanus toxin.
- Each milligram of crystallized toxin contains 50–57 million mouse lethal doses.
- The extreme toxicity is the reason that an attack of tetanus does not confer immunity, as the total dose of tetanus toxin is less than the amount required to provoke an immune response.

Epidemiology

- Tetanus is a major cause of mortality in unvaccinated persons and newborns of unvaccinated mothers (especially in newborns with contaminated umbilicus with tetanus spores).
- Tetanus may be associated with dirty and contaminated wounds, thorn pricks and ear piercing.
- Incubation period is usually 2–14 days after injury (range may be as short as one day in case of serious infection or as long as 51 days).
- Tetanus is not a communicable disease.

Pathogenesis

- Spores of *C. tetani* are introduced in the wound, which are converted to vegetative forms. Vegetative organisms produce an exotoxin tetanospasmin under low ambient oxygen (anaerobic conditions).
- Tetano-spasmin binds irreversibly to motor neurons at neuro-muscular junction and it travels retrograde towards the CNS where it inhibits spinal presynaptic inhibitory synapses (i.e. inhibit acetylcholine release).
- Net result is the loss of inhibitory neurons, which manifests as spasm of agonists and antagonist muscles. This results in muscle contraction, characteristic localized spasms, and rigidity.
- Toxin has no effect on conscious level, however autonomic dysfunction can occur characterized by tachycardia, arrhythmias, labile hypertension, cutaneous vaso-constriction, etc.
- Once the toxin is attached to neurons, it cannot be neutralized by antitoxin.
- In newborn infants contamination of umbilical cord is the commonest source of infection whereas in older children deep punctured wounds cause tetanus.

Clinical findings

- There are many clinical forms of tetanus:
  - Localized tetanus
  - Generalized tetanus
  - Cephalic tetanus
  - Tetanus neonatorum (neonatal or umbilical tetanus)

Tetanus neonatorum

- Usually symptoms begin 3–10 days after birth and pattern is generalized.
- Initial symptom is failure to suck and inability to open the mouth known as trismus or lockjaw.
- As baby gets hungry he starts crying excessively, becomes restless and irritable.
- Spasm of the facial muscles immobilizes the jaw and produces a fixed sardonic grin called risus sardonicus.
- Within 12–24 hours after the first symptom generalized tonic muscular convulsions occur producing flexion and adduction of the arms, clenching of the fists and extension of the lower extremities.

- Initially spasms are mild but later become severe with spasms of the glottis and respiratory muscles leading to asphyxia and cyanosis.
- Abdominal muscles become rigid and spasms of the muscles of the back may result in opisthotonos.
- Spasms may be precipitated by touch, noise or bright light but baby is fully conscious during spasms.
- Baby may develop high temperature and jaundice with septic umbilicus.
- Involuntary defecation and urination may occur but more commonly there is constipation and urinary retention.
- Baby may die during severe spasms from exhaustion, heart failure or retention of respiratory secretions and bronchopneumonia.
- Signs and symptoms increase during first 3–7 days of illness, and then become stable during second week and in those cases who survive, these symptoms gradually subside in 2–6 weeks.

Localized tetanus

- In the proximity of the injury, there is pain, continuous rigidity, and spasm of the muscles.
- It resolves within weeks without any sequelae.
- This is rare in children with fatality rate of 1%.

Generalized tetanus

- This is the most common form of tetanus in children and also in newborns (tetanus neonatorum).
- The characteristic of seizures or spasms in tetanus is that they may be initiated by a stimulus. Any stimulus such as slight noise, light, or touch may initiate the tetanic spasm.
- Trismus or lock jaw (difficulty in opening the mouth) is present in about 50% of cases as presenting symptom. It is due to masseter muscle spasm.
- Other symptoms are minimal pain at the site of inoculation, restlessness, irritability, headache, stiff neck, difficulty in swallowing, lock jaw (spasm of masseter muscle), risus sardonicus (facial distortion resembles a grimace due to intractable spasms of facial and buccal muscles), and opisthotonos (an arched posture which may be so severe that only head and heels touch the ground).
- There may be spasm of laryngeal or respiratory muscles leading to airway obstruction and asphyxia necessitating artificial ventilation.
- Spasms may cause fractures and local hemorrhages.
- As there are no sensory or cortical function disturbances, patients remain conscious during spasm and feels extreme pain.
- Autonomic disturbances may be tachycardia, arrhythmias, labile hypertension, sweating, urinary retention, and cutaneous vasoconstriction.

Cephalic tetanus

- This rare form is due to any injury near the head (e.g. otitis media, trauma to the head and face, and nasal foreign bodies).
- In this form incubation period is short (1–2 days).
- Cranial nerve involvement is the most characteristic feature of this form of tetanus.

Diagnosis

- Diagnosis of tetanus is mainly clinical.
- In tetanus neonatorum, babies are mostly delivered at home, are approximately 7 days old, they fail to suck, develop trismus and muscular spasms and their sensorium is clear.
- In a child, a history of a wound or bite, the characteristic facial appearance, and muscle spasm help in the diagnosis.
- History of non-vaccination is present in most cases.
- Laboratory studies are of little value and are usually normal.
- Blood count and cerebrospinal fluid are normal. There may be occasional leukocytosis on complete blood examination, which is due to secondary bacterial infection or stress of tetanic spasms.
- Blood sugar and calcium level are normal. EEG (electroencephalogram) or EMG (electromyogram) is normal. Gram stain of *C. tetani* is positive in only 1/3rd of cases.

Management

- Aims of treatment are to:
  - Remove the source of exotoxin (tetanospasmin).
  - Neutralize remaining circulating toxin before it reaches the CNS and fixes to the neural tissue.
  - Provide supportive care until tetanospasmin is metabolized.

Specific measures

Anti-toxin

- It is given as soon as possible to neutralize the toxin which is present in the circulation to prevent its binding with the neural tissue. Once tetanus toxin starts axonal ascent to the spinal cord, it cannot be neutralized by the anti-toxin.
- To neutralize circulating toxin give **horse Anti-Tetanus Serum (ATS)** 50,000–100,000 units (half dose is given intramuscularly and half is given intravenously); but at minimum (especially in newborns) 10,000 units may be required.
- Serum sickness is the main side effect of ATS (in 15% of cases).
- **Human Tetanus Immune Globulin (TIG)** 3000–6000 units intramuscularly as a single dose is the treatment of choice to neutralize the circulating toxin because it has longer half-life of 30 days and there is no chance of serum sickness.

- Minimum single dose of TIG (especially in newborns) is 500 units intramuscularly. It is unnecessary to give TIG directly into the wound.

Antibiotics

- Give crystalline Penicillin 200,000 units/kg/day in four divided doses for 10–14 days to kill vegetative *C. tetani*.
- Other antibiotics may be given instead of penicillin. Metronidazole is equally effective in a dose of 500 mg 8 hourly. Erythromycin or tetracyclin (after 8 years of age) are used in patients allergic to penicillin.

Supportive measures

Sedation

- All patients with generalized tetanus need muscle relaxants. Give Injection diazepam 0.1–0.2 mg/kg intravenously every 3–6 hours to control muscle spasm.
- Magnesium sulfate, other benzodiazepines, chlorpromazine, dantrolene, and baclofen are also used.
- Add chlorpromazine (largectil) syrup 10–15 mg/kg/day to control fits.
- Phenobarbitone or paraldehyde may be given.
- An adequately sedated child is one whose respiration is not depressed and occasional muscular spasm is acceptable. Over-sedation is represented by shallow respiration and diminution of muscle tone.

Feeding

- Give feeding by nasogastric tube ½ oz. every hour during 1st week and then 1 oz every 2 hours till oral feeding is possible.
- Daily milk requirement is around 100–120 ml/kg/day.

Nursing care

- Clean the umbilicus in the newborn or wound in infants and children and place the patient in a quiet environment free from noise and visual stimuli.
- Change the posture and observe for apneic spells.
- Cardiorespiratory monitoring, and frequent suctioning, is important.
- Mouth, skin, bladder, and bowel care is necessary.
- If need arises give artificial respiration.

Complications

- Aspiration of secretions and pneumonia
- Lacerations of mouth and tongue due to seizures
- Vertebral fractures during seizures
- Decubitus ulceration
- Autonomic disturbances

Prevention

Tetanus neonatorum

- Conduct the deliveries in the hospital.
- Train the 'dais' for aseptic technique.
- Immunize the baby following disease, as it does not confer immunity.
- Immunize the mother during pregnancy by giving 2 injections of tetanus toxoid 4 weeks apart in the second trimester of pregnancy. Last injection should be given at least 4 weeks before delivery. Antibodies transferred to the baby protect against neonatal tetanus. If mother has been immunized previously against tetanus, then one injection of tetanus toxoid during pregnancy is sufficient.
- It is not recommended to excise the umbilical stump in neonatal tetanus.

Tetanus in children

- Active immunization with tetanus toxoid is the mainstay of the prevention of tetanus. After three doses of vaccine, a protective level of serum anti-toxin is almost always achieved (0.01 units/ml). If an older child gets some wound, the indication for active and passive immunoprophylaxis depends on the previous immunization status of the child and the severity of the wound. A booster dose of toxoid at the time of injury is needed in a vaccinated child if no tetanus vaccine booster has been given in the last 5 years (or within 3 years in a case of a heavily contaminated wound). Anti-toxin is given in un-immunized or incompletely vaccinated children with soil-contaminated wounds. Tetanus toxoid and anti-toxin should be given at the same time but at different sites using separate syringes.
- Immediate and thorough surgical treatment of wounds is very important.
- Immunize the child after disease as it doses not confer immunity.

Prognosis

- Fatality rate mainly depends on the quality of supportive care.
- Main causes of death are respiratory failure and pneumonia.
- Mortality rate is 60% or greater for tetanus neonatorum, and 20–50% in children. Most mortality occurs in the first week of illness.

Good prognostic factors are

- Incubation period of 8–10 days
- Progression longer than 60 hours
- Absence of fever
- Local disease
- Survival for 10 days

Poor prognostic factors are

- Duration between the injury and the onset of trismus less than 7 days.
- Duration between trismus and the onset of generalized tetanic spasms less than 3 days.

BOTULISM

CASE

A previously healthy 4-month-old infant develops ***generalized weakness*** with ***difficulty in sucking***, swallowing, and ***constipation***. There is no history of fever. Mother is treating the child with honey. On examination, he has ***poor head control***, a ***weak cry*** and expressionless face. Cerebrospinal fluid analysis is normal. Nerve conduction velocity and sensory nerve function are normal.

- Botulism is a paralytic disease resulting from ingestion of tasteless toxin in tin food that has been prepared at temperature insufficient to kill spores (115°C) and then stored at room temperature.
- *Clostridium botulinum*is anaerobic, gram-positive, spore-forming soil bacillus that produces powerful neurotoxin that prevents acetylcholine release at myoneural junctions.

Clinical findings

- The incubation period for food-borne botulism is 8–36 hours.
- There is lethargy, headache, double vision, dilated pupils, ptosis, dysphagia, dysarthria, and descending skeletal paralysis. Death is from respiratory failure.
- Classic triad important for diagnosis is :
    - Afebrile
    - Symmetrical descending paralysis with bulbar palsies
    - Clear sensorium
- Toxin can be identified in stool, gastric aspirate, serum or suspected food.
- Most laboratory tests including CSF are normal.
- Infant botulism is characterized by constipation, generalized hypotonia, progressing to respiratory failure.
- The clostridia producing infant botulism have been isolated from honey given to an infant.
- Spores in dust from nearby construction sites may contaminate household utensils and cause infection.

Differential diagnosis

- Guillain-Barré syndrome (there is ascending paralysis, sensory deficits, increased CSF protein).
- Poliomyelitis, diphtheritic polyneuritis (both have increased CSF protein).
- Tick paralysis (there is ascending motor paralysis).
- Myasthenia gravis (mostly in adolescent girls with ocular and bulbar symptoms, normal pupils, fluctuating weakness).

Management

- Supportive care, especially respiratory (e.g. ventilation) and nutritional.
- Give antitoxin for food-borne botulism.
- Human botulinum immune globulin for infant botulism.
- Aminoglycoside antimicrobials and clindamycin may exacerbate neuromuscular blockage and should be avoided.

Prognosis

- Mortality rate is about 6%.
- Symptoms subside over 2–3 months with complete recovery expected.
- Immunity to botulism toxin does not develop, even with severe disease.

MEASLES

CASE

A 2-year-old boy presents with ***fever***, ***cough***, blocked runny nose (***coryza***) and sticky eyes (***conjunctivitis***) for 4 days. Now, he has developed a ***maculopapular rash*** around his ears and hair line. Rash is continuing to spread over most of his body. He has ***Koplik spots*** on buccal mucosa. He is miserable and lethargic for the last 5 days. On examination, temperature is 104°F. There is no respiratory distress but he is coughing. Pharynx is red. He has exudative conjunctivitis.

Definition

- Measles is an acute, highly contagious viral disease, characterized by a final stage of maculopapular rash erupting successively over the neck, face, body, arms, and legs and is accompanied by a high-grade fever.

Etiology

- Measles is an RNA virus.
- Virus is present in the nasopharyngeal secretions, blood, and urine during the prodromal stage and for short time after the appearance of maculopapular rash.

Epidemiology

- Measles is a worldwide disease. Both epidemic and endemic existence is known. Highest incidence is in winter.
- Mode of transmission is by direct or indirect contact and droplet spray.
- The period of infectivity is 3 days before and 6 days after the appearance of rash.
- It is a frequent cause of ill health and morbidity in malnourished children below the age of 3 years.
- It is unusual below the age of 4 to 6 months (some protection may persist up to the age of 9 months) due to the protection provided by the maternal antibodies.
- In healthy children it runs a benign course.

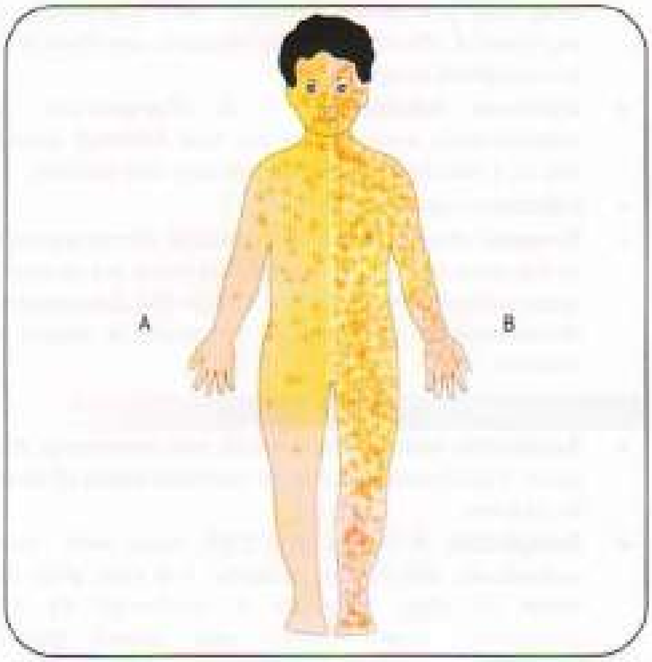


Figure 10.9: Distribution of measles rash. (A) side shows the early rash over the upper part of the body. The (B) side shows the next stage of rash covering the whole body.

Pathology

- The essential lesion is in the skin, respiratory tract, intestinal tract and conjunctivae.
- There is serous exudate and proliferation of polys and mononclear cells around capillaries. Koplik spots consist of serous exudate and proliferation of endothelial cells.
- There is lymphoid hyperplasia with the formation of multinucleated giant cells known as Warthin Finkeldey reticuloendothelial giant cell.
- Interstitial pneumonitis due to measles may form Hecht giant cell pneumonia.
- In fatal cases of encephalomyelitis there is perivascular demyelinization of areas of the brain and spinal cord.
- In subactue sclerosing panencephalitis (SSPE), degeneration of the cortex and white matter with intranuclear and intracytoplasmic, inclusion bodies may occur.

Clinical findings

- The incubation period is 10–12 days.
- The history of contact with a patient of measles can usually be elicited.
- There are three clinical stages of measles:
  1. Incubation stage
  2. Prodromal stage (Koplik spots and mild symptoms)
  3. Maculopapular rash stage accompanied by high-grade fever
- The prodromal phase, which usually lasts 3 to 5 days and is characterized by high fever and lassitude, which persists and is accompanied by cough, coryza and conjunctivitis over next 3 days. The cough is barking and harsh and more noticeable at night.
- Rash precede Koplik spots, which are present on intensely red base on the buccal mucosa and tend to occur opposite the lower molars. They disappear within 12–18 hours. Posterior cervical lymphadenopathy may accompany these early manifestations. This phase is also called catarrhal phase.
- At the onset of maculopapular stage, temperature rises abruptly and reaches 40° to 40.5°C (104°-105°F).
- The rash usually starts as faint macules on the face behind the ears and along the hairline.
- The lesions become increasingly maculopapular as the rash spreads to the trunk and limbs. As it finally reaches the legs and feet on the second or third day it begins to fade on the face. The fading of rash proceeds downwards in the same sequence as its appearance

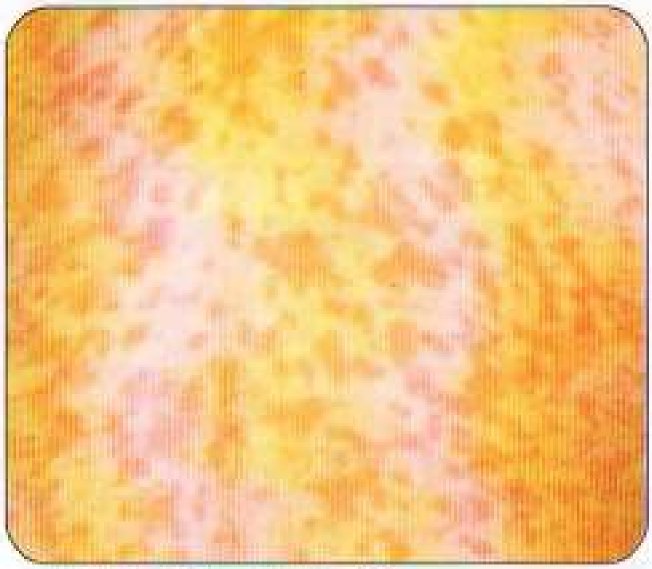


Figure 10.10: Typical rash in measles.

- Posterior cervical lymphadenopathy and slight splenomegaly may be present.
- There may be abdominal pain due to mesenteric lymphadenopathy.
- The severity of the disease is directly related to the extent and confluence of the rash. In severe measles the face is swollen and disfigured.
- Hemorrhagic measles or black measles is a severe form in which rash is in confluent ecchymoses. Bleeding may occur from the mouth, nose or bowel and death may result before the rash has appeared. As the rash fades there is branny desquamation and brownish discoloration, which disappear within 7 to 10 days. The general appearance (the patient is red eyed, with puffy eyelids and swollen bridge of the nose and copious thin nasal discharge with a distressed look) is known as measly look.

Inapparent measles infection

- A subclinical form of measles may occur in individuals with passively acquired antibody, such as infants and recipients of blood products.
- In such a case, rash may be indistinct, brief, or sometimes entirely absent.
- In some children who have received vaccine, when exposed to measles, may have a rash but few other symptoms.
- Children with inapparent or subclinical measles do not transmit measles virus and disease to other contacts.

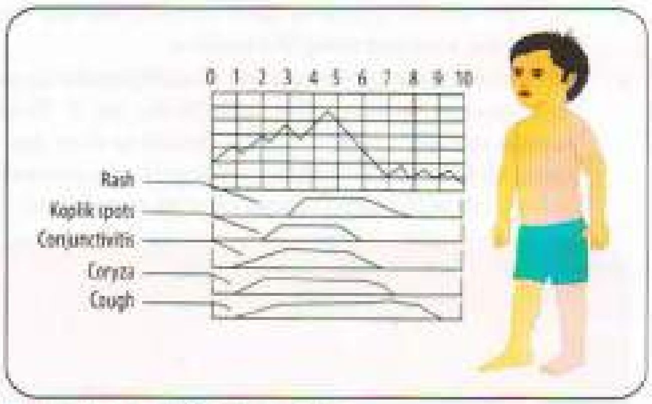


Figure 10.11: Stages of measles.

Diagnosis

- Diagnosis is primarily clinical.
- During the prodromal stage, multinucleated giant cells can be demonstrated in smears of nasal mucosa.
- Virus can be isolated in tissue culture or antibody titer can be detected in serum.
- White blood cell count is low with relative lymphocytosis.
- Lumbar puncture in encephalitis shows an increase in protein and a small increase in lymphocytes.

Differential diagnosis

- Typical measles is unlikely to be confused with other illnesses, especially if Koplik spots are observed.
- **Roseola infantum (exanthem subitum).** In this when rash appears fever subsides as against measles in which temperature also rises with the appearance of rash.
- **Rubella, Echo and Coxsackie infections.** In these rash is less striking than that of measles, fever and severity of illness is also less. There are no koplik spots and lymphadenopathy may be prominent.
- **Scarlet fever.** The rash of scarlet fever is diffuse, finely papular with a sandpaper feel most marked on the abdomen.
- **Meningococcemia.** It may be accompanied by maculopapular rash but more commonly it is petechial with marked toxicity and hypotension but cough and conjunctivitis are usually absent.
- **Drug rash** and **serum sickness**. There is a history of ingestion of offending drug or injection and there is no accompanied cough.
- **Erythema infectiosum.** It is characterized by erythematous eruption on the face followed after 1 day by a maculopapular eruption with lacy pattern.
- **Infectious mononucleosis.**
- **Kawasaki disease.** Kawasaki syndrome can cause many of the same findings as measles but there are no Koplik spots and a severe prodromal cough. The characteristic thrombocytosis of Kawasaki syndrome is absent in measles.

Complications

- **Respiratory system:** Otitis media and pneumonia may occur. Pneumonia is the most common cause of death in measles.
- **Encephalitis:** It occurs in 1:1000 cases with coma, convulsions and bizarre behavior 3–8 days after the onset of rash. Diagnosis is confirmed by CSF pleocytosis, raised protein and normal glucose content.
- **Hemorrhagic (black) measles:** In fulminant measles hemorrhage may occur into GIT, mucous membrane and CNS. Fever and toxicity is pronounced.
- **Thromobocytopenia** may occur with bleeding into the rash.
- **GIT complications:** Post measles gastroenteritis is common, often with a fatal outcome. Noma or gangrene of mouth may occur.
- **Eye:** Corneal ulceration, conjunctivitis and optic nerve damage may occur rarely.
- **Heart:** Myocarditis and cardiac failure occur occasionally.
- **Miscellaneous:** Measles leads to immunosuppresion and may cause flaring up of quiescent tuberculosis or pyogenic infections. Anergy to tuberculin is frequent. Nephrosis, eczema and asthma may abate after measles infection. Extreme marasmus and kwashiorkor may develop after measles.

Management

- Treatment is mainly supportive.
- Good nursing care is essential.
- There is no specific antiviral therapy.
- Antipyretics (paracetamol or ibuprofen) for high fever, relief of cough, maintenance of clear nasal passages, sedatives, bed rest and adequate fluid intake are essential.
- Humidification of the room may relieve the irritating cough by making the room comfortably warm.
- Bacterial super infections should be treated with antimicrobial therapy.
- Complications should be treated accordingly.
- Gamma globulin and steroid are of limited value.

Role of vitamin A in measles

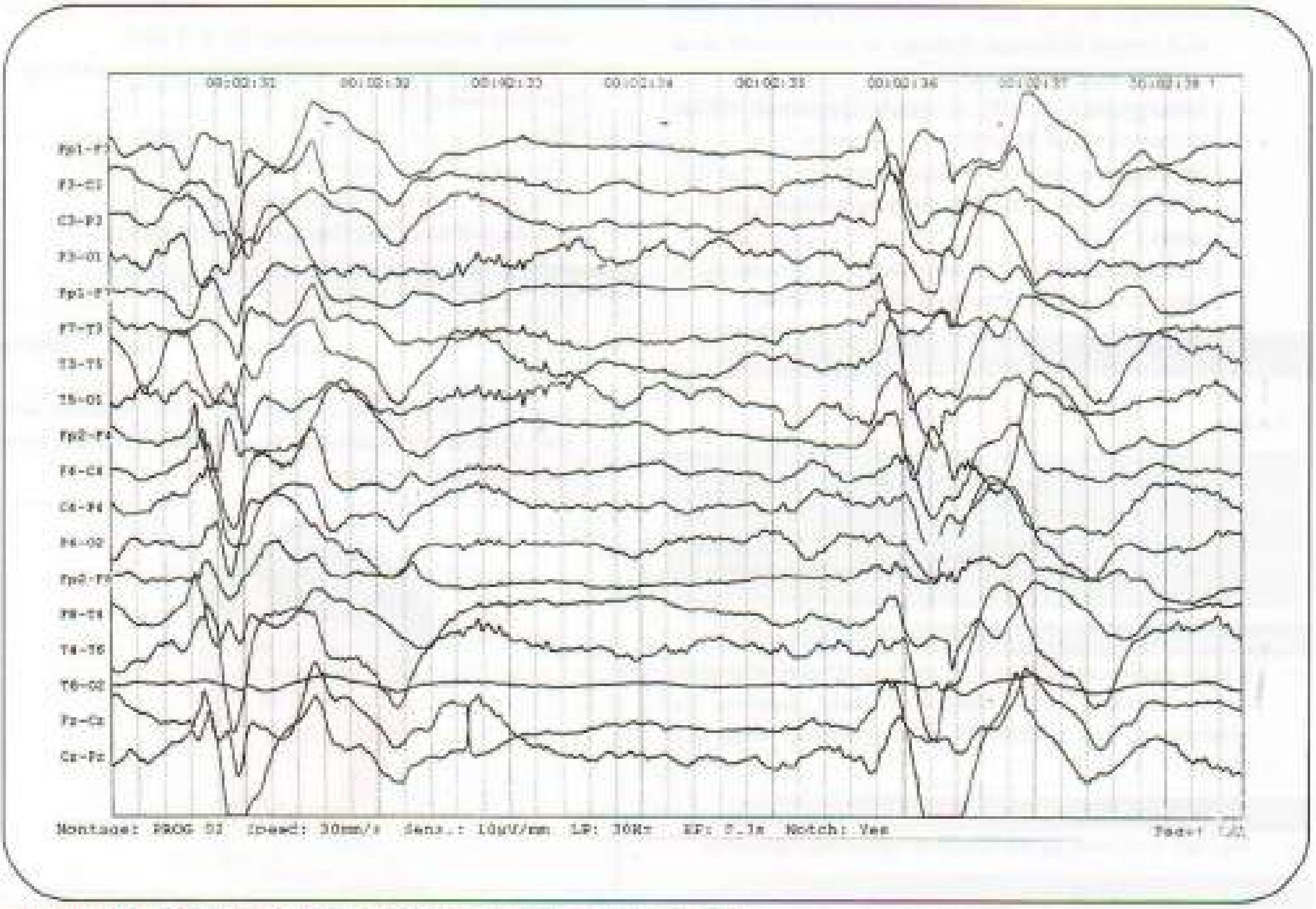
- It has been observed that giving vitamin A can reduce morbidity and mortality of measles.
- Vitamin A therapy is indicated for all patients with measles.
- Vitamin A should be administered once daily for 2 days:
    - 200,000 IU (for children 12 months of age or older
    - 100,000 IU for infants 6 months through 11 months of age
    - 50,000 IU for infants younger than 6 months of age
- In children with signs and symptoms of vitamin A deficiency, a 3rd dose according to age is recommended 2–4 weeks after the 2nd dose.

Prognosis

- It is a self-limited disease lasting 7–10 days often without sequelae.
- Common causes of death are pneumonia and secondary bacterial infections.
- Encephalitis may cause disability or death in 40% of cases.
- Progressive CNS degeneration may lead to subacute Sclerosing Panencephalitis (SSPE) ending in death.

Prevention

- Patients with measles shed virus from 7 days after exposure to 4–6 days after the onset of rash. Exposure to patients with measles should be avoided during this period.
- Attenuated measles vaccine affords 95% protection against natural disease.
- Immunity appears to be life-long.
- Attenuated live measles vaccine (Moratan strain) should be administered at 3–9 months of age.
- If vaccine is given up to 3 days (72 hours) after exposure to natural disease, it can be prevented by successful immunization, as incubation period of vaccine is 7 days while that of natural disease is 10 days.
- If exposure has already occurred then give measles immune globulin 0.25 ml/kg within 6 days after exposure.
- Immune globulin is indicated for susceptible household contacts of measles patients:
    - Infants younger than 6 months of age
    - Pregnant women
    - Immunocompromised persons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T5-O1
Fp2-F4
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C4-P4
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Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
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Figure 10.12: Characteistic EEG in subacute sclerosing panencephalitis.

CASE

SSPE: A 10-year-old boy presents with deteriorating school performance and psychosocial withdrawal for last 8 months. There are episodes of ***abnormal behavior***. On examination, he has hypertonia, sluggish reflexes and ***myoclonic jerks***. There is ***suppression burst pattern*** on EEG.

- **SSPE**: Subacute Sclerosing Pan-encephalitis is chronic encephalitis caused by persistent measles virus infection of the CNS.
    - This is late onset outcome of measles but is always fatal.
    - An altered measles virus is harbored intracellularly in the CNS for 7–10 years when virus regains virulence and attacks the cells of CNS.
    - This causes inflammation and cell death leading to neurodegenerative process in CNS.
    - Measles at an early age (before 2–4 years) favors the development of SSPE.
    - Initially, there are behavior changes and leading to massive myclonic jerks, choreoathetoid movement and dystonia (damage to basal ganglia).
    - Diagnosis is confirmed by: measles antibody detected in CSF, suppression burst pattern on EEG and typical histologic findings or isolation of virus antigen on brain tissue biopsy.
    - Management of SSPE is mainly supportive similar to care in other degenerative diseases.
    - Isoprinosine (with or without interferon) has 30–34% remission rate and can be continued for 1–2 years.
    - Carbamezepine is effective in controlling myoclonic jerks in the early stages of illness.

MUMPS

CASE

A 12-year-old boy presents with ***fever***, muscular pain, headache, and malaise. There is ***bilateral swelling*** in front of his earlobe (over the area from the back of his mandible). Taking sour liquid causes pain on swelling.

Definition

- It is an acute contagious viral disease, characterized by fever, bilateral or unilateral parotid swelling or tenderness, and sometimes meningoencephalitis and orchitis.

Etiology

- Mumps is caused by a RNA virus called mumps virus.

Epidemiology

- It occurs commonly in the 5–10 year age group.
- It is transmitted by direct contact, by droplet infection, and by fomites contaminated with saliva.
- It equally affects the males and females.

Pathogenesis

- Virus enters the cells of the respiratory tract and multiplies there.
- After the last multiplication, virus enters into the blood and infects many tissues but salivary glands are selectively affected.
- There is edema and infiltration with lymphocytes in the affected glands. Inclusion bodies are absent.

Clinical findings

- The incubation period is 12–25 days.
- The period of maximum infectiousness is 1–2 days before to 5 days after onset of parotid swelling.
- About 40% of infections are sub-clinical. In most cases there are very few symptoms except swelling of one of the salivary glands. The most common site is the parotid gland, but submaxillary and submental salivary glands may be less commonly involved.
- With parotid gland involvement, the lobe of the ear is displaced upward and outward. Characteristically the swelling obliterates the angle of the jaw.
- Usually swelling is painful; pain is especially felt by tasting sour food. Swelling increases very rapidly. Within a few hours maximum swelling occurs but swelling continues to increase for 1–3 days.
- There is redness and swelling around the opening of the Stensen duct.
- There may be edema of soft palate, larynx and pharynx. Edema may extend up to upper chest.
- There may be no or low-grade fever.
- Within 3–7 days, swelling gradually subsides.

Diagnosis

- Diagnosis is generally clinical.
- Usually there is leukopenia with relative lymphocytosis.
- Serum amylase level is elevated. Level increases with the gradual increase in the swelling and becomes normal within 2 weeks.

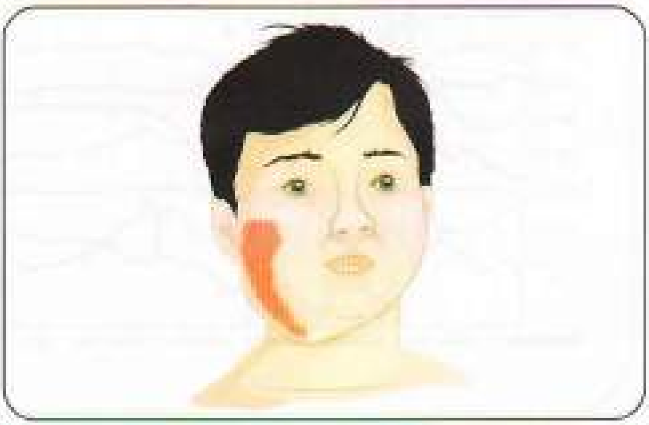


Figure 10.13: Showing enlargement of the parotid gland.

- The virus can be isolated from the saliva, CSF, blood or urine by a virus culture.
- Enzyme immunoassay for mumps IgG and IgM may be used to diagnose the mumps. IgM antibodies are present in acute illness (in the first few days), may be raised for weeks to months and are diagnostic.

Differential diagnosis

- **Parotitis due to other viruses** (parainfluenza 1 and parainfluenza 3 viruses, influenza A virus, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus and HIV).
- **Cervical adenitis:** The lymph node has a well-defined, discrete border which is firm and tender.
- **Suppurative (purulent) parotitis:** Usually it is unilateral. The gland surface is red, warm and there is tenderness. Pus can be expressed from Stensen's duct. Main organism involved is Staphylococcus aureus. There is increased WBC count.
- **Recurrent parotitis:** Frequent recurrent swelling of the parotid gland as a consequence of drugs such as iodides and phenothiazines or idiopathic causes may occur but it is not tender.
- **Tumors:** These are rare and can cause confusion in the early stages of malignancy
- **Obstruction** of the Stensen duct
- **Collagen vascular diseases** such as Sjögren syndrome
- **Systemic lupus erythematosus**

Complications

- **Meningoencephalomyelitis:** It may be a primary infection of the neurons or may be due to post-infectious encephalitis with demyelination. It may be seen in 10% of cases of mumps, but CSF pleocytosis may be seen in about 65% of patients of parotitis. It follows the parotitis by 3 to 10 days. Sometimes it precedes the swelling of salivary glands.
- **Epididymo-orchitis:** This is quite common in the adult male but is uncommon in pre-pubertal boys. It is generally unilateral and occurs in the first week of parotitis. Fever, nausea, vomiting, abdominal pain are followed by swollen and tender testis. The average duration of illness is 4 days. Involvement is bilateral in 30% of cases. Affected testes may atrophy in 30–40% of cases but sterility is still rare.
- **Pancreatitis:** It is severe but uncommon manifestation. There is epigastric pain, tenderness with fever and chills.
- **Deafness:** This is rare and caused by neuritis of the auditory nerve.
- **Miscellaneous complications:** These include oophoritis (in females), thyroiditis, myocarditis, or arthritis.

Management

- Treatment is generally supportive.
- There is no specific antiviral treatment available.
- In case of fever, antipyretics are given (paracetamol or ibuprofen).
- Semi-solid or liquid diet is given to avoid pain on chewing.
- Bed rest may be needed in some cases especially if there is orchitis.
- Local support is also given in orchitis.

Prognosis

- Recovery is the rule.
- Even meningo-encephalitis is generally mild and benign.

Prevention

- Passive protection is not indicated.
- Children should be vaccinated (MMR at age 12–15 months.

CHICKENPOX (Varicella)

CASE

A 7-year-old ***unimmunized child*** presents with ***fever*** of 104°F (40°C). There is ***vesicular rash***. Some lesions are umblicated and crusted.

- Chickenpox is a common childhood exanthem caused by human herpes virus Varicella-Zoster Virus (VZV).
- After chickenpox, immunity is life-long.
- When a person recovers from chickenpox, the virus remains in the dorsal root (sensory) ganglion cells in a latent state for decades. As immunity decreases in late adulthood, the virus may reactivates (in 10–15% of cases) and causes the dermatomal exanthem called herpes zoster or shingles.

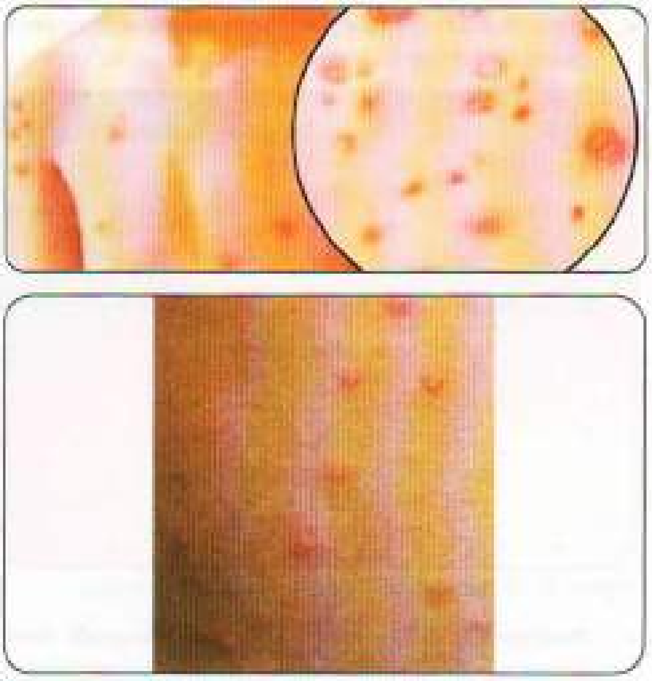


Figure 10.14: Characteristic rash in chicken pox.

Pathogenesis

- VZV is one of the severe human herpes-viruses. It is a DNA virus.
- Incubation period (the interval between infection and appearance of the vesicular rash) is usually 14–15 days (range is 10–20 days).
- Initial site of infection is the conjunctivae or upper respiratory tract.
- The virus then replicates for about 4 to 6 days at a local site in the head or neck.
- Thereafter, virus is transmitted throughout the body (primary viremia).
- Virus is released in large amounts 1 week later after a second replication (secondary viremia) and invades the cutaneous tissues.
- When the virus leaves the capillaries and enters the epidermis, vesicles of chickenpox appear on the skin.

Transmission

- Chickenpox is transmitted by droplets in respiratory secretions. Air currents from an infected child to a susceptible child carry these water droplets.
- Varicella is contagious from 24–48 hours before the rash appears and while un-crusted vesicles are present, which is usually 3–7 days.

Clinical findings

- The characteristic feature of chickenpox is the vesicle.
- Exanthem develops over 3–6 days. Usually, it begins along the hairline on the face. Rash begins as red macules that progresses to tiny vesicles with surrounding erythema (dew drops on a rose petal), form pustules, become crusted, scabbed over, and leave no scar. The rash then appears in successive crops over the trunk, and then the extremities.
- In the first week, there are lesions in different stages of development (up to 5 crops of lesions may be seen).

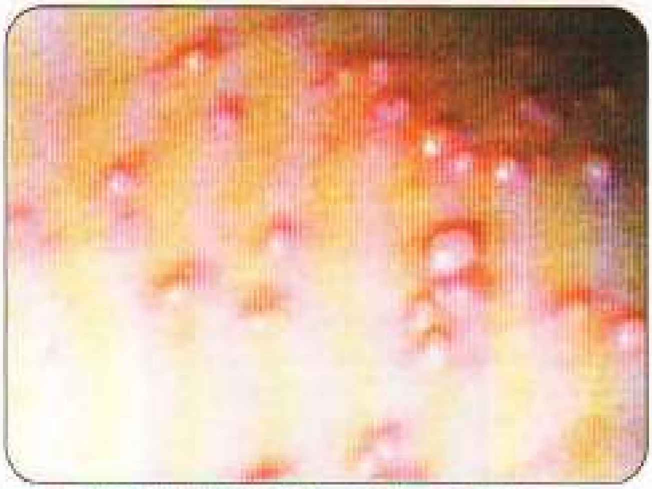


Figure 10.15: Lesions of chicken pox in initial stages.

- Prodrome is mild with malaise and low-grade fever. Temperature rises when pox appears. Temperature is rarely above 102°F. Secondary cases (having an infected sibling) have a more severe disease.
- Child becomes afebrile by the end of the first week and the cutaneous lesions starts crusting and become dry and fall off.
- Infants have more severe disease but due to persisting maternal antibody, chickenpox in the first few months may be mild. Children on high-dose corticosteroid therapy are at greater risk of fatal chickenpox.

Complications

- **Bacterial infection** of a vesicular lesion is the most frequent complication of chickenpox. Common infecting organisms are *Group A Streptococcus* and *Staphylococcus*. Less common but more serious bacterial infections are toxic shock syndrome, sepsis, cellulitis, erysipelas, cutaneous abscesses, impetigo, and suppurative lymphadenitis.
- **Viral sequelae** of chickenpox may involve all systems. Most common are pneumonitis (cough, dyspnea, tachypnea, rales, and cyanosis are seen several days after the onset of rash), hepatitis, arthritis, pericarditis, glomerulonephritis, orchitis and involvement of CNS (encephalitis). Encephalitis occurs in less than 0.1% of cases, usually in the first week of the illness. It presents as cerebellitis with ataxia and resolves completely.
- **Reye's syndrome** (protracted vomiting or a change in sensorium with a history of salicylate use).
- **Progressive varicella:**
    - Progressive varicella is characterized by visceral organ involvement, coagulopathy, severe hemorrhage, and continued vesicular lesion development after 7 days.
    - It is a severe complication of primary VZV infection.

Diagnosis

- Diagnosis is usually apparent on clinical examination (characteristic vesicular rash).
- Leukocyte counts are normal or low. Leukocytosis suggests secondary bacterial infection.
- On X-ray, in varicella pneumonia, there are numerous bilateral nodular densities and hyperinflation.
- Virus can be identified by obtaining samples of the vesicle fluid for inoculation in cell culture.
- The most reliable methods for testing VZV humoral immunity are Fluorescent Antibody to Membrane Antigen (FAMA) and Enzyme-Linked Immunosorbent Assay (ELISA).

Differential diagnosis

- Varicella-like rash may be present in:
    - **Coxsackie-virus infection.** There are fewer lesions and there is no crusting.
    - **Impetigo.** There are fewer lesions, perioral or peripheral lesions, and no classic vesicles. Lesions respond to antimicrobial agents.

  - **Papular urticaria.** There is history of insect bite and rash is non-vesicular.
  - **Scabies.** There are burrows and no typical vesicles.

Management

- Chickenpox in healthy child is usually not a serious disease.
- Maintenance of hydration is important.
- Fever is usually low-grade and can be treated with paracetamol. Aspirin should not be given to avoid the risk of Reye's syndrome.
- Calamine lotion may be applied on skin to relieve severe pruritus. Diphenhydramine syrup may be given orally to relieve discomfort of itching.
- General hygiene measures should be maintained by keeping the nails trimmed and clean and skin cleanliness.
- Antibiotics are given for secondary skin infection.
- For immunocompromised child or a child on corticosteroid therapy, VZIG should be given.

Acyclovir

- Acyclovir therapy is not recommended routinely for treatment of uncomplicated varicella in the otherwise healthy child.
- Oral therapy with acyclovir (20 mg/kg/dose (maximum 800 mg/dose) is given as 4 doses/day for 5 days.
- Oral acyclovir is used to treat uncomplicated varicella in individuals at increased risk for moderate to severe varicella:
  - Nonpregnant individuals older than 12 years of age
  - Children older than 12 months of age with chronic cutaneous or pulmonary disorders
  - Children receiving corticosteroid therapy
  - Children receiving longterm salicylate therapy
- To be most effective, treatment should be initiated as early as possible (preferably within 24 hours of the onset of the rash). There is less benefit if treatment is initiated 72 hours after the onset of the rash.
- Intravenous acyclovir therapyis indicated for severe disease and for varicella in immunocompromised children. IV acyclovir therapy ($500\ mg/m^2$ every 8 hour) initiated within 72 hours of development of initial symptoms).
- Treatment is continued for 7–10 days or until no new varicella lesions have appeared for 48 hours.

Prevention

- Disease can be prevented by varicella vaccine.

Postexposure prophylaxis

- Vaccine given to healthy children (as soon as possible) within 3 or 5 days after exposure is effective in preventing or modifying varicella.
- Varicella vaccine is also recommended for outbreak control.
- Newborns whose mothers demonstrate varicella 5 days before to 2 days after delivery should receive varicella immunoglobulin (VariZIG):
  - 0.5 vial for those weighing ≤2 kg
  - 1 vial for those weighing >2 kg)

Prognosis

- Mortality rate in children is about 1:50,000, and in infants (<1 year age) is 1:13,000.

Neonatal varicella

- Mortality is high in neonates born to mothers who contracted varicella around the time of delivery.
- Infants whose mothers demonstrate varicella in the period from 5 days prior to delivery to 2 days after delivery are at high risk for severe varicella.
- These infants get the infection transplacentally as a result of maternal viremia (which may occur up to 48 hours prior to onset of maternal rash).
- Infant may present with varicella rash usually from 2nd day of life to the 2nd week of life.
- Newborns whose mothers develop varicella during the period of 5 days before to 2 days after delivery should receive Varicella Zoster Immunoglobulin (VZIG) as soon as possible.
- If VZIG is not available, Intravenou Immunoglobulin (IVIG) may provide some protection.
- As perinatally acquired varicella may be life threatening, the infant should be treated with acyclovir (10 mg/kg every 8 hours IV) when lesions develop. It is preferable to initiate treatment with oral acyclovir in infants who received VZIG.

Congenital varicella syndrome

- In utero transmission of Varicella Zoster Virus (VZV) can occur. About 25% of the fetuses may become infected when pregnant women do contract varicella early in pregnancy.
- The congenital varicella syndrome occurs in infants born to women who have varicella during pregnancy:
  - Before 13 weeks of gestation (about 0.4% of infants).
  - Between 13–20 weeks of gestation (about 2% of infants).
  - After 20 weeks of gestation (Rare cases of congenital varicella in infants reported).
- The congenital varicella syndrome is characterized by:
  - Cicatricial skin scarring in a zoster-like distribution
  - Limb hypoplasia
  - Abnormalities of the neurologic system (e.g. microcephaly, cortical atrophy, seizures, and mental retardation)
  - Abnormalities in eyes (e.g. chorioretinitis, microphthalmia, and cataracts)
  - Abnormalities of renal system (e.g. hydroureter and hydronephrosis)

  - Abnormities of autonomic nervous system (neurogenic bladder, swallowing dysfunction, and aspiration pneumonia)
  - Low birthweight
- The diagnosis of VZV fetopathy is based on:
  - History of gestational varicella
  - Presence of characteristic abnormalities in the newborn infant
- Viral DNA may be detected in tissue samples by Polymerase Chain Reaction (PCR).
- VZV-specific IgM antibody is detectable in the cord blood sample in some infants.
- A persistently positive VZV IgG antibody titer at 12–18 months of age is an indicator of prenatal infection in the asymptomatic child.
- Development of zoster in the 1st year of life without evidence of postnatal infection is also an indicator of prenatal infection.
- VZIG is the treatment administered to the susceptible mother exposed to varicella to modify maternal disease severity.
- Similarly, acyclovir treatment may be added to the mother with severe varicella.

INFECTIOUS MONONUCLEOSIS

CASE

A 12-year-old girl presents with a 3-week history of high-grade ***fever***, ***sore throat*** and fatigue. She is taking ***ampicillin***. Now, she has developed a morbilliform ***rash***. Physical examination reveals marked cervical ***lymphadenopathy***, and enlarged exudative tonsils. ***Spleen is palpable*** 2 cm below the left costal margin. There is increased white blood cell count and differential that has 50% lymphocytes (***10% atypical***). ***Monospot test*** is ***positive***.

- It is the most common syndrome associated with *Epstein–Barr Virus* (EBV).
- It is transmitted in saliva from asymptomatic patients.

Clinical findings

- Incubation period is about 1–2 months.
- There is malaise, and anorexia for 1–2 days, then fever, exudative pharyngitis (in 50% cases), enlarged lymph nodes, splenomegaly (50–75%) hepatomegaly (30%) with hepatitis and rash (macular, scarlentiform, or urticarial) develops.
- Rash is almost universal in patients taking penicillin or ampicillin.

Diagnosis

- **Complete blood count:** Leucopenia (☐WBC) may occur early.
- Atypical lymphocytes accounting for 10% of white cells.
- **Heterophil antibodies (Paul Bunnell antibodies):** Positive heterophile antibodies (Mono spot test) in 90% of older children but unreliable in children <5 years.
- Anti-EBV antibodies: Measure immunoglobulin M (IgM) antibody to viral capsid (VCA) when diagnosis in doubt.
- EBV PCR: This detects EBV DNA. It is the method of choice for the diagnosis of CNS and ocular infections.

Differential diagnosis

- Severe pharyngitis may suggest group A streptococcal infection
- Severe primary herpes simplex pharyngitis
- Similar illnesses that produce atypical lymphocytosis include:
  - Rubella (pharyngitis not prominent, shorter illness, less adenopathy and splenomegaly)
  - Adenovirus (upper respiratory symptoms and cough, conjunctivitis, less adenopathy, fewer atypical lymphocytes)
  - Hepatitis A or B (more severe liver function abnormalities, no pharyngitis, no lymphadenopathy)
  - Toxoplasmosis (negative heterophil test, less pharyngitis)
- Serum sickness-like drug reactions
- Leukemia (smear morphology is diagnostic)
- CMV mononucleosis (minimal pharyngitis and less adenopathy)

Complications

- Splenic rupture
- Hematologic complications (hemolytic anemia, thrombocytopenia, and neutropenia)
- Neurologic involvement (aseptic meningitis, encephalitis, isolated neuropathy such as Bell palsy, and Guillain-Barre syndrome)
- Rare complications include myocarditis, pericarditis, and atypical pneumonia
- Recurrence or persistence of EBV-associated symptoms for 6 months or longer is called chronic active EBV infection

Management

- There is no specific treatment for infectious mononucleosis.
- Supportive treatment includes fluid and nutritional support. Antipyretics are given.
- Rest and symptomatic treatment is needed.
- Acyclovir and corticosteroids, decrease viral replication. But this does not reduce the severity or duration of symptoms of disease.
- Avoid contact sports due to risk for rupture of spleen (during first 2–3 weeks of illness or while splenomegaly is present).

- Short courses of corticosteroids (<2 weeks) may be helpful for complications (airway obstruction, thrombocytopenia, autoimmune hemolytic anemia, seizures). Prednisolone is given 1 mg/kg/day for 7 days.
- In immunocompromised patients with chronic EBV infection, treat with acyclovir, valacyclovir, penciclovir, ganciclovir, or foscarnet.

MALARIA

CASE

A 5-year-old child from a village presents with ***fever*** (2 weeks duration) ***every other day*** along with nausea, vomiting, arthralgia, and abdominal pain. There is history of ***rigors*** with fever and sweats when the fever breaks. On clinical examination, heart rate is 120 beats/minute, respiratory rate is 45 breaths/minute, and temperature is 104° F. There is no rash or lymphadenopathy. Spleen is 3 cm palpable (***splenomegaly***).

- Malaria is a common acute or chronic infectious cause of morbidity in tropical and semi-tropical regions of the world.
- The illness is caused by any one of the five species of *Plasmodium* parasite and is characterized by recurrent high-grade fever, splenomegaly, and anemia.

Malarial parasite and its life cycle

- Malarial parasite is an obligate intracellular protozoan.
- There are five species:
  1. Plasmodium falciparum (most virulent)
  2. Plasmodium vivax (most common)
  3. Plasmodium malariae
  4. Plasmodium ovale
  5. Plasmodium knowlesi

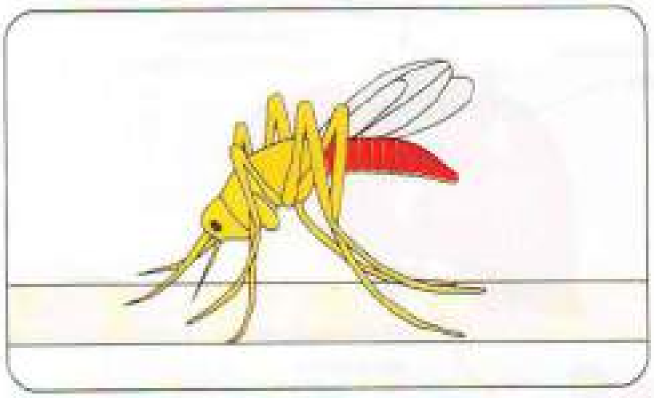


Figure 10.16: A female Anopheles mosquito.

- Life cycle of the mosquito is completed in the human host (asexual phase) and also in the mosquito vector (sexual phase).
- When a female *Anopheles* mosquito feeds on blood of an infected person, the part of the life cycle of malarial parasite begins and malarial gametocytes ingested with the blood form *zygote* in the gut of the mosquito.
- *Zygotes* mature and migrate to the mosquito salivary glands where they remain as *sporozoites*.
- When a female mosquito bites the healthy person, *sporozoites* are inoculated in the blood stream of that person. Antibody (but not drug therapy) decreases *sporozoite* infectivity.
- *Sporozoites* leave the blood stream immediately (within minutes) and enter the hepatocytes (exo-erythrocyte or intrahepatic phase). Here parasite forms a cystic structure (after multiple asexual divisions) called a *schizont*.
- After 1–2 weeks, the *schizont* ruptures, thus releasing thousands of infective *merozoites* into the blood stream. In P. *falciparum* or *P. malariae* infection, all *shcizonts* rupture so there is no *schizont* in the liver. In P. vivax and P. ovale infection, some of the *schizonts* remain in liver (called *hypnozoites*) and may rupture months to years later (malarial relapse).
- After leaving from the liver, *merozoites* enter the circulating RBCs (erythrocytic phase).
- Inside the RBC, the protozoan is called a *trophozoite* (ring form) and appears as blue signet ring against the pink cytoplasm of the RBC. In the RBC, a mature *trophozoite* is formed.
- Nuclear (asexual) division of *trophozoiteoccurs* creating *schizonts*, which contains 6–24 merozoites.
- When RBC ruptures, *merozoites* are released and enter uninfected RBCs to start a new erythrocytic cycle.
- Some *merozoites* do not enter the RBCs and differentiate into sexual (male and female) *gametocytes*.
- The next mosquito may ingest these gametocytes, so in this way life cycle is completed.

Transmission/epidemiology

- Standing water and warm climate favour mosquito propagation and endemicity.
- For the spread of malaria, anopheline vector, infected and susceptible hosts are the pre-requisites.
- Due to the presence of mutant gene, most of the endemic areas have *Chloroquine-ResistantP. Falciparum (CRPF)*.
- Malaria can also be spread through direct exposure to infected blood transfusion, or contaminated needles.
- Congenital malaria appears in young infants born to a mother who carried the infection during pregnancy.
- In both transfusion induced and congenital malaria, *merozoites* are introduced directly, so the exo-erythrocytic (intrahepatic) phase does not occur.
- Most malarial deaths occur in infants and young children.

Pathophysiology

- Symptoms of malaria appear only when RBCs rupture.

- Fever is the most remarkable symptom when erythrocytes rupture and merozoites are released into the circulation. Production of tumor necrosis factor or other cytokines are responsible for fever. There is peripheral vasodilatation in response to fever and due to vasoactive material produced by malarial parasite.
- Hypoglycemia is due to decreased glycogen stores, impaired gluconeogenesis, and increased glucose consumption by the malarial parasites.
- Splenomegaly is an important feature of malaria. RBCs infected with plasmodium lose their deformability. There is increased trapping in the splenic cords causing enlargement of spleen. There is marked activation of reticuloendothelial system. Splenic macrophages phagocytize the infected RBCs and become hyperplastic. Splenic rupture may occur due to vascular congestion.
- Anemia is mainly due to RBC hemolysis (greatest in *P. falciparum* due to heavy parasitemia) splenic sequestration of RBCs and malarial bone marrow depression.
- Due to massive hemolysis, there may be hyperkalemia, hyperbilirubinemia, hemoglobinemia, and hemoglobinuria.
- Infected RBCs become rigid and sticky blocking the passage through capillaries (adherence to endothelium of capillaries is due to knobs on RBCs membrane). Blood flow become sluggish as more and more cells and debris accumulate causing local tissue hypoxia. This phenomenon is responsible for complications of falciparum malaria (e.g. cerebral malaria, pulmonary edema, renal failure, and intestinal malabsorption or sloughing).
- There are many defects of red blood cells causing the erythrocyte membrane resistant to invasion and cytoplasm inhospitable to parasite growth. These genetic erythrocyte defects include thalassemia, sickle cell trait, G6PD deficiency, and pyruvate kinase deficiency. Children lacking the Duffy blood group are naturally resistant to *P. vivax*.

Clinical findings

- Clinical features are variable depending on the species involved, patient's age, and immune status. Symptoms are most severe in malaria due to *P. falciparum*.
- In endemic areas, young infants may be relatively protected due to transmission of maternal antibody and high concentration of HbF. Young children are more susceptible to severe infection.
- Due to repeated malarial parasite infection, individuals may get immune and have mild symptoms even in the presence of heavy parasitemia.

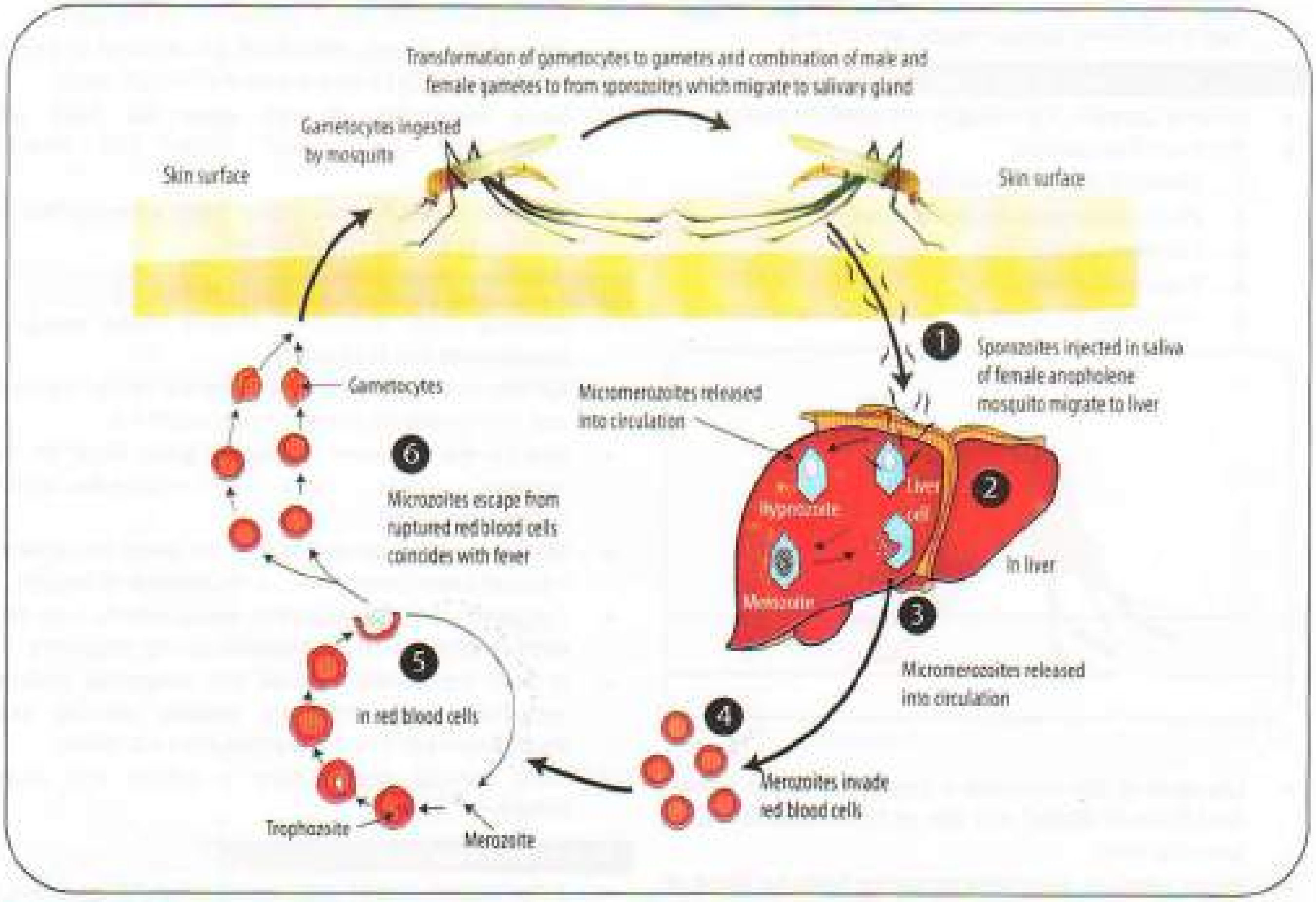

Transformation of gametocytes to gametes and combination of male and female gametes to from sporozoites which migrate to salivary gland
Gametocytes ingested by mosquito
Skin surface
Skin surface
1
Sporozoites injected in saliva of female anopholene mosquito migrate to liver
Gametocytes
Micromerozoites released into circulation
6
Microzoites escape from ruptured red blood cells coincides with fever
Hypnozoite
Liver cell
2
In liver
Merozoite
3
Micromerozoites released into circulation
5
in red blood cells
4
Merozoites invade red blood cells
Trophozoite
Merozoite

Figure 10.17: Life cycle of malarial parasite.

- During erythrocytic rupture, patient experiences a brief episode of chills followed by high fever, headache, nausea, vomiting, myalgia, and delirium.
- This paroxysm classically returns after 48–72 hours depending on the *Plasmodium* species. Children usually do not show the characteristic fever pattern. They usually have continuous or intermittent fever.
- There may be splenomegaly, which may be massively enlarged.
- Other findings include orthostatic hypotension, dehydration, jaundice, herpes labialis, and pallor due to anemia.
- There are non-specific findings in case of congenital malaria. Symptoms usually occur at the end of first month of life. Presentation may be same as a case of sepsis (fever, lethargy, irritability, anorexia, diarrhea, jaundice, and hepatosplenomegaly).
- Malarial relapse may occur in case of *P. vivax* or *P. ovale*.
- Infection during pregnancy may cause intra-uterine growth retardation or premature delivery.

Congenital malaria

- Congenital malaria is acquired from the mother prenatally or perinatally.
- Congenital malaria may cause abortions, miscarriages, stillbirths, premature births, intrauterine growth retardation, and neonatal deaths.
- Congenital malaria usually occurs in the offspring of a nonimmune mother with malaria.
- The first sign or symptom may occur between 14 hours to several months of age (usually 10 and 30 days of age).
- Clinical findings include fever, restlessness, drowsiness, pallor, jaundice, poor feeding, vomiting, diarrhea, cyanosis, and hepatosplenomegaly.
- Malaria is often severe during pregnancy and may cause intrauterine growth retardation and low birthweight, even in the absence of transmission from mother to child.

Table 10.12: Incubation period of malarial parasite.

Species	Incubation period
P. falciparum	9–14 days
P. vivax	12–17 days
P. ovale	16–18 days
P. malariae	18–40 days

Table 10.13: World Health Organization criteria for severe malaria.

- Impaired consciousness
- Prostration
- Respiratory distress
- Multiple seizures
- Jaundice
- Hemoglobinuria
- Abnormal bleeding
- Severe anemia
- Circulatory collapse
- Pulmonary edema

Diagnosis

- Clinical history and examination is very important for the diagnosis of malaria (triad of fever, splenomegaly, and anemia).
- The diagnosis of malaria is established by identification of organisms on Giemsa-stained smears of peripheral blood.
- Thick smear is done first for screening parasitemia. Multiple thick smears are obtained several times a day (every 4–6 hours) up to 3 consecutive days. If a single blood smear is negative, it does not exclude the diagnosis of malaria and blood smears are repeated. If infected RBCs are seen on thick smear, a thin smear helps species identification (by morphology of intra-cellular *trophozoites*). High parasitemia (more than 10% infected erythrocytes or more than 500,000 infected erythrocytes/μL) is associated with high morbidity and mortality. Treatment response is monitored by daily examination of malarial parasite (MP) slides for parasitemia. Constant or increased number of infected RBCs after 48 hours of treatment shows treatment failure.
- Most symptomatic patients with malaria will have detectable parasites on thick blood smears within 48 hours.
- For nonimmune persons, symptoms typically occur 1–2 days before parasites are detectable on blood smear.
- Normochromic, normocytic anemia with increased reticulocyte count may be present.

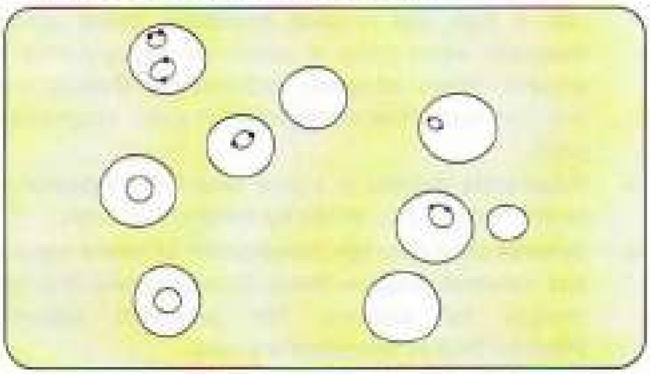


Figure 10.18: Thin film showing malarial parasite.

- Total leukocyte count and differential counts are normal with increased proportion of monocytes.
- Hypoglycemia is a common finding.

Differential diagnosis

It depends on the presenting signs and symptoms of the malaria.

- Pneumonia

- Meningitis. Encephalitis
- Appendicitis
- Gastroenteritis
- Hepatitis.
- Enteric (typhoid) fever
- Tuberculosis
- Septicemia
- Endocarditis
- Brucellosis
- Leptospirosis
- Pyelonephritis
- Amebic liver abscess
- Hodgkin disease
- Collagen vascular disease
- Babesiosis

Complications

- Mostly, complications are due to P. falciparum infection. Diagnosis of *P. falciparum* malaria is a medical emergency. Malarial infection from other species is usually benign.
- The most common complications in children are severe anemia, impaired consciousness (including cerebral malaria), respiratory distress (a result of metabolic acidosis), multiple seizures, prostration, and jaundice.
- Severe malarial anemia (hemoglobin level <5 g/dL) is the most common severe complication of malaria in children.
- **Cerebral malaria** is defined as the presence of coma in a child with *P. falciparum* parasitemia and an absence of other reasons for coma. This is the most serious complication. It usually manifests as headache, diminished level of consciousness, prolonged seizures, coma, or other neurologic changes. CSF pressure is raised but CSF examination is usually normal. Mortality rate is high and residual neurologic deficit occurs especially when there is associated hypoglycemia is present. When adequate anti-malarial therapy and intensive supportive management is given, prognosis is good.
- **Respiratory distress** is a poor prognostic indicator in severe malaria. It is caused by metabolic acidosis.
- **Seizures** are a common complication of severe malaria and cerebral malaria. Benzodiazepines are first-line therapy for seizures. For persistent seizures, phenobarbital or phenytoin are used.
- **Hypoglycemia** is a complication of malaria. It is more common in children, pregnant women, and patients receiving quinine therapy.
- **Circulatory collapse (algid malaria)** manifests as hypotension, hypothermia, rapid weak pulse, shallow breathing, pallor, and vascular collapse. Death may occur within hours.
- **Long-term cognitive impairment** occurs in 25% of children with cerebral malaria.
- **Tropical splenomegaly syndrome** is a chronic complication of *P. falciparum* malaria. In this case massive splenomegaly persists after treatment of acute infection. It is characterized by marked splenomegaly, hepatomegaly, anemia, and an elevated immunoglobulin M level. It is caused by an impaired immune response to P. falciparum antigens. Prolonged (for many years) antimalarial prophylaxis is needed to treat this condition.
- **Prostration** is characterized by inability to sit, stand, or eat without support, in the absence of impaired consciousness.
- Other complications are:
  - ○ Black-water-fever (hemoglobinuria) is due to massive hemolysis. Urine appears dark and acute renal failure may occur. Hypersensitivity to quinine may also be responsible
  - ○ Jaundice
  - ○ High output congestive heart failure
  - ○ Disseminated Intravascular Coagulation (DIC).
  - ○ Nephrotic syndrome (by *P. malariae*)

Management

Supportive care

- Volume depletion should be corrected
- Analgesics and antipyretics are given
- Blood transfusion for anemia

Specific measures

- Anti-malarial treatment should be started immediately once the diagnosis of malaria is made. Delay in treatment may adversely affect the prognosis especially in *P. falciparum* malaria. A response to treatment is defined as a decrease in daily parasitemia.
- Artemether is given 3.2 mg/kg by immediate intramuscular injection, followed by 1.6 mg/kg daily for 3 days.
- Chloroquine affects the erythrocytic parasites only. Chloroquine is the drug of choice in chloroqine-sensitive *Plasmodium*. Chloroquine is given 10 mg base per kg immediately, followed by 5 mg/kg base at 6, 24 and 48 hour.
- If the parasite count does not drop rapidly (within 24–48 hours) or does not become negative within 4 days, it shows chloroquine-resistant malaria and the patient is given a different antimalarial regimen.
- For chloroquine-resistant *P. falciparum*, Quinine dihydrochloride 20 mg salt per kg is infused during 4 hours, followed by maintenance of 10 mg salt per kg infused during 2–8 hours every 8 hours for 3 days.
- Parenterally administered artemether can be substituted for quinine for treatment of severe malaria in children.
- Patients from areas with chloroquine-resistant *P. falciparum* who have mild infection, parasitemia less than 1%, no evidence of complications, and no

vomiting and who can take oral medication can be given oral therapy with either oral atovaquone-proguanil, oral artemether-lumefantrine, or oral quinine plus doxycycline, tetracycline, or clindamycin.

Table 10.14: Treatment of malaria

Atovaquone+proguanil (tab 250 mg+100 mg) (pediatric tablet 62.5 mg+25 mg)	
5–8 kg	2 ped tab PO qid for 3 days
9–10 kg	3 ped tab PO qid for 3 days
11–20 kg	1 adult tab PO qid for 3 days
21–30 kg	2 adult tab PO qid for 3 days
31–40 kg	3 adult tab PO qid for 3 days
>40 kg	4 adult tab PO qid for 3 days
Artemether+lumefantrine (tab 20 mg+120 mg)(1st dose followed by 2nd dose 8 hours later then 1 dose bid for 2 days	
5–15 kg	1 tab per dose
15–25 kg	2 tab per dose
25–35 kg	3 tab per dose
≥35 kg	4 tab per dose
Quinine sulphate plus one of the following: Quinine sulphate 8.3 mg/kg base or 10 mg/kg salt PO tid for 3–7 days is	
Doxycycline	2.2 mg/kg PO every 12 hours for 7 days
Clindamycin	20 mg base/kg/day tid for 7 days
Tetracycline	25 mg/kg/day qid for 7 days
Mefloquine 13.7 mg base/kg/day (15 mg salt/kg) initial dose. 2nd dose 9.1 mg base/kg (10 mg salt/kg) given 6–12 hours later.	

- Primaquine kills both hepatic and erythrocytic parasites. Quinine also attacks both phases.
- In case of severe malaria, exchange transfusion may be a life-saving procedure especially if the patient is non-immune and parasitemia is more than 15%.

Treatment of complications

- Anemia, seizures, pulmonary edema, and renal failure are treated accordingly.

Prevention

Environmental protection (avoiding mosquito [illegible]

- Wear long clothing
- Cover exposed areas of the body with insect repellents
- Remain in screened-areas, and using fine mesh mosquito netting around beds
- Mospel may be applied to clothing for extra protection.

Chemoprophylactic drugs

- Chemoprophylactic drugs are given once weekly, starting 1–2 weeks before going to endemic area, continuing throughout the stay, and ending 4 weeks after leaving the endemic area.
- Chloroquine is the drug of choice and is taken orally 5 mg base/kg.
- For chloroquine resistant *P. falciparum*, the drug of choice is mefloquine.
- Doxycycline is given in patients older than 8 years of age who do not tolerate mefloquine. Doxycycline should be started 1–2 days prior to departure and continued for 4 weeks after last exposure.
- Daily primaquine is also effective in chloroquine resistant *P. falciparum*, and is also effective to prevent relapse of *P. vivax* or *P. ovale*.

All the above drugs do not guarantee the protection from the malaria infection.

Table 10.15: Chemoprophylaxis of malaria.

Drug	Dosage
Chloroquine-sensitive areas Chloroquine	5 mg base/kg/week up to 300 mg (adult dose)
Chloroquine-resistant areas Mefloquine	Once a week <10 kg: 4.6 mg base (5 mg salt)/kg/week ¼ tablet (10–19 kg) ½ tablet (20–30 kg) ¾ tablet (21–45 kg) 1 tablet (>45 kg)
Doxycycline	2 mg/kg/day (age >8 years) up to 100 mg (adult dose)
Relapse of P. vivax or P. ovale Primaquine	0.3 mg base/kg/day up to 15 mg (adult dose) during the last 2 weeks of prophylaxis.

TUBERCULOSIS

A 5-year-old boy presents with history of ***fever*** and ***weight loss*** for ***three weeks***. Chest radiograph reveals right upper lobe collapse and consolidation and ***hilar lymphadenopathy***. Mantoux test reveals 20 mm induration.

- Tuberculosis remains the second leading cause of death (after HIV) from an infectious disease worldwide (WHO).
- Almost one-third of the world's population (2.5 billion people) is infected with *M. tuberculosis.*
- Currently Pakistan stands 5th amongst the 22 high TB burden countries which account for about 81% of all estimated TB cases around the world.
- According to WHO, the incidence of sputum positive TB cases in Pakistan is 97/100,000 per year and for all types it is 231/100,000 or around 420,000 new cases each year.

Definitions

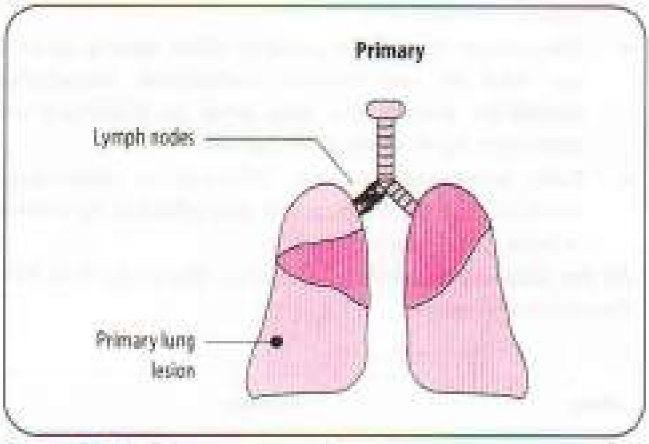


Figure 10.19: Primary tuberculous lesion.

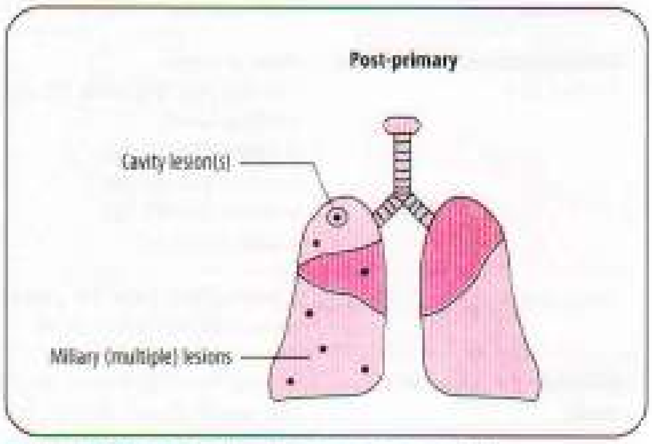


Figure 10.20: Post-primary tuberculous lesion.

Primary tuberculosis

- It is the first time infection in a previously uninfected child. There are two types.

Primary complex

- It is the first time infection in a child where the bacilli are taken to the regional lymph nodes (the site of main activity).
- Basic lesion formed during the primary infection are primary focus (Ghon's focus), lymphangitis, and lymphadenitis. This is collectively called the primary complex.

Progressive primary complex

- It is the extension of the disease beyond the primary focus and the regional node by bronchogenic or hematogenous spread.

Secondary tuberculosis

- It is the active tuberculosis, which can occur any time after the primary infection or disease, due to endogenous or exogenous re-infection.

Tuberculosis control

- Tuberculosis control means less than 1% tuberculin positivity among children in the age group of 0–14 years.

Etiology

- It is caused by the *Mycobacterium tuberculosis.*
- Tubercle bacilli are non-spore forming, non-motile, weakly gram-positive rods, and obligate aerobes.
- The characteristic of all mycobacteria is that they are acid-fast (resist discoloration by acid dyes). The cell wall of mycobacteria mostly contains lipids. This lipid-rich cell wall is responsible for acid fastness and resistance to the bactericidal actions of antibody and complement.

Transmission

- Infection is usually transmitted from person to person by the inhalation of infective droplet nuclei that result from aerosolization of respiratory secretions.
- The source of the infected material is usually an adult with cavitary pulmonary tuberculosis.
- The most important factors determining the infectivity are the concentration of the organisms in the sputum and the closeness and duration of contact with the index case.
- There will be increased chance of transmission to others when the patient has:
- Positive sputum smear for acid-fast bacilli
- An extensive upper lobe infiltrate or cavity
- Copious production of thin sputum
- Severe and forceful cough
- The poor air circulation enhances transmission of M. tuberculosis.
- Patient usually becomes non-infectious within 2 weeks after starting adequate anti-tuberculous treatment.
- It is very uncommon that young children may infect other children and adults because in young children, tubercle bacilli are present in very small number in endo-bronchial secretions and cough is not so forceful to make infectious particles of sufficient size in the air to infect others.
- Older children with adult-type pulmonary tuberculosis may transmit the tubercle bacilli to other people.

Pathogenesis

- Local inflammatory reaction follows and histocytes begin to carry the organisms to the regional lymph nodes forming a primary (Ghon) complex. In 98% of cases, lung is the portal of entry.

- Within the alveoli multiplication of tubercle bacilli occurs. Mostly, the bacilli are killed by the macrophages in the alveolar ducts and alveoli. Some bacilli may survive within the non-activated macrophages. These macrophages carry the tubercle bacilli to the regional lymph nodes through lymphatic vessels.
- Most commonly, the hilar lymph nodes are involved. If the upper lobe of the lung is involved, this may drain into para-tracheal lymph nodes.
- Tubercle bacilli spread by the blood stream and lymphatics to many parts of the body when the primary complex is developing.
- When a large number of bacilli are disseminated, miliary tuberculosis may occur.
- Cell mediated immunity usually develops after 4–8 weeks. At this time, the primary complex usually heals completely due to fibrosis or calcification and undergoes to caseous necrosis and encapsulation. Viable *M. tuberculosis* may persist for many years within these foci.
- The involved lymph nodes may remain normal in size in most of the cases but they may occasionally enlarge and cause partial obstruction of the bronchus leading to the hyperinflation of the lung portion distal to the partial obstruction. If obstruction is complete, there may be atelectasis in the distal segment of the lung.
- Central caseation in primary focus may rupture into a bronchus resulting in pneumonia.
- Calcification due to healing may disappear in 3–5 years.
- In extensive caseation, there may be a cavity formation due to liquefaction of the center of the lesion and drainage through the bronchus.
- There is considerable variability between initial infection and clinically apparent disease. Massive lymphohematogenous spread causing miliary or acute meningeal tuberculosis occurs 3–6 months after the initial infection.

Clinical findings

Pulmonary tuberculosis

- Initial symptoms are fever, anorexia, irritability, malaise, easy fatigability weight loss and night sweats. Some children may show signs and symptoms of an upper respiratory tract infection.
- On X-ray, mediastinal lymphadenopathy or classic pulmonary infiltrate with hilar adenopathy may be demonstrated. It may manifests as lobar pneumonia with high-grade fever, cough and respiratory distress, dullness on percussion, increased breath sounds and moist rales. Even in untreated patients these symptoms last for 1–2 weeks.

Tuberculous pleural effusion

- Tuberculous pleurisy is common complication in primary tuberculosis. It is almost a component of the primary complex. It is usually unilateral but may be bilateral.
- It originates when there is discharge of bacilli from a caseated lymph node or a subpleural pulmonary focus into the pleural space.
- It occurs within 6–12 months after initial infection and patient presents with cough, pleuritic pain, and shortness of breath and signs of fluid in the chest.
- Spontaneous resolution may occur within 3–4 weeks or following aspiration but radiographic findings may persist for months.

Reactivation or post–primary TB

- Healed lesions may become site of active bacterial multiplication usually involving apices (apical seedings or Simon foci). These lesions caseate and liquefy forming cavities.
- It may lead to progressive pulmonary disease or complications like pulmonary hemorrhage, bronchial ulceration, spontaneous pneumothorax, pleurisy, empyema, bronchiectasis, and intestinal and miliary tuberculosis.

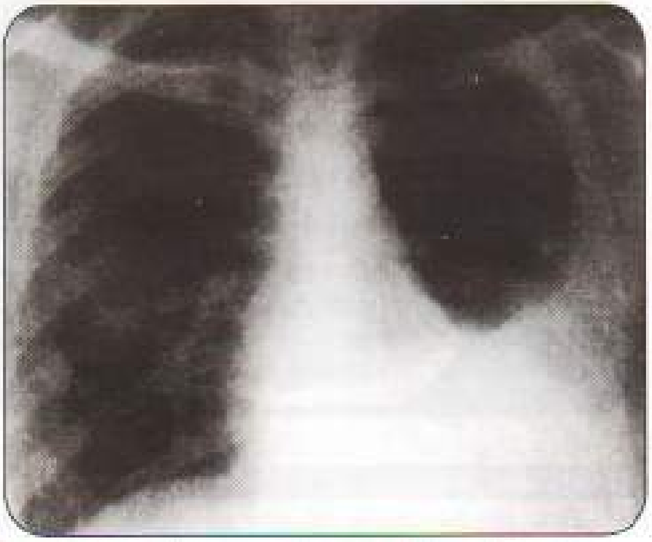


Figure 10.21: Pulmonary tuberculosis (pleural effusion)

Miliary tuberculosis

- Miliary tuberculosis is defined as release of massive numbers of tubercle bacilli into the bloodstream, resulting in simultaneous disease in two or more organs.
- It occurs within 3–6 months after formation of the primary complex and usually is an complication of primary infection.
- Mostly, lungs, spleen, liver, and bone marrow is involved.
- There is weight loss, anorexia, malaise, and low-grade fever. After several weeks, hepatosplenomegaly and generalized lymphadenopathy develops in about 50%

of the cases. At this stage, fever may be high-grade (39°C–40°C).

- Chest X-ray may be normal or show evidence of a primary complex. After 3–4 weeks of onset of symptoms, lung fields are filled with tubercles. Other findings such as respiratory distress, rales, wheezing, pneumothorax, pneumomediastinum, or pleural effusions may be present.
- Headache indicates meningitis in a patient with miliary tuberculosis.
- Abdominal pain or tenderness indicates tuberculous peritonitis in a patient with miliary tuberculosis.
- In different studies, 13–87% of the patients with miliary tuberculosis have choroid tubercles.
- Diagnosis depends upon high index of suspicion. About 30% of these patients have a negative tuberculin skin test. Chest X-ray shows typical miliary shadows.
- Resolution of miliary tuberculosis may be slow even with proper treatment, but most patients recover completely. Fever usually settles within 2–3 weeks. Chest X-ray findings may resolve after several months.

Tuberculous meningitis

- (This is discussed in detail in chapter of central nervous system).

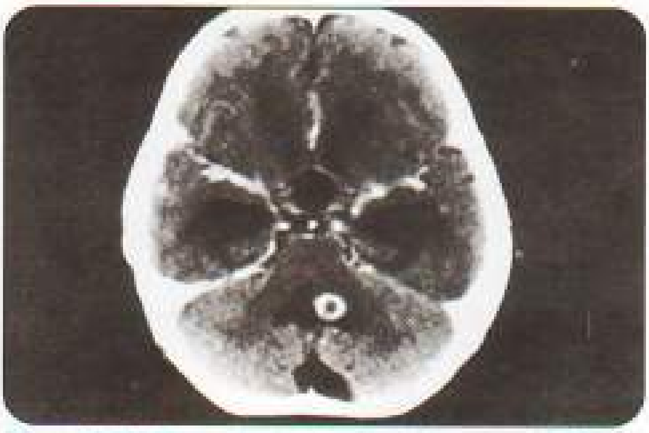


Figure 10.22: CT scan brain showing lesions due to TBM.

Skeletal tuberculosis

- Early in the course of primary infection, skeletal tuberculosis occurs due to the lymphohematogenous dissemination of tubercle bacilli.
- Bone infection may occur rarely due to the direct extension of tubercle bacilli from a contiguous lymph node.
- Pathologic process usually begins in the metaphysis because of its rich blood supply. There is the formation of the granulation tissue and caseation leading to bone destruction by the direct infection and pressure necrosis.
- Infection may be extended involving the joint. Most commonly the vertebrae are affected leading to tuberculosis of the spine (Pott's disease). Thoracic vertebrae (especially the T_{12}) are commonly involved. Body of the vertebrae is usually involved leading to destruction and collapse.
- On X-ray, there is narrowing of the disc space and wedging of the vertebral body causing the angulation of the spine (gibbus) or kyphosis.
- There may be low-grade fever, restlessness, pain, abnormal posturing, or abnormal gait.

Abdominal tuberculosis

- Tuberculous enteritis is caused by ingestion of infected milk, hematogenous spread, or super-infection of the gut mucosa by swallowed tubercle bacilli in the sputum.
- Most commonly jejunum and ileum are affected (near the Peyer patches).
- Shallow ulcers are formed in the gut causing the pain, diarrhea/constipation, and weight loss.
- Mesenteric adenitis may cause intestinal obstruction or even peritonitis due to erosion through the omentum.
- Generalized tuberculous peritonitis may occur due to hematogenous dissemination. There may be a palpable irregular non-tender mass with doughy feeling due to the matted lymph nodes, omentum, and peritoneum. There may be ascites associated with fever.
- Tuberculin skin test is almost always positive.
- Paracentesis is diagnostic.

Renal tuberculosis

- Renal tuberculosis is rare in children because it takes many years to develop after the primary infection.
- Tubercle bacilli spread through lymphohematogenous dissemination, reach the kidney, and form small caseous tubercles in the renal parenchyma.
- Infection may spread and involve the ureter, gallbladder, prostate, or epididymis.
- Initially, there are no symptoms. Progressively, there may be sterile pyuria, hematuria, dysuria, or vague flank pain.
- Urine culture is positive for *M. tuberculosis*.
- Tuberculin skin test should be positive.

Superficial lymph node tuberculosis

- Tuberculosis of the superficial lymph nodes is called **scrofula**.
- It is the most common type of the extra-thoracic disease. It occurs in 3–6% of primary infections.
- Mostly, it is the early manifestation of lymphohematogenous dissemination. It occurs within 6–9 months of the primary infection. Regional lymphadenopathy is the part of the primary complex of tuberculosis.
- Initially, the lymph nodes are firm, discrete, and non-tender. There may be low-grade fever. Gradually, the lymph nodes enlarge.
- When the skin ruptures, a sinus tract is formed.

- Lymphadenitis due to *M. tuberculosis* responds well to the anti-tuberculous treatment.

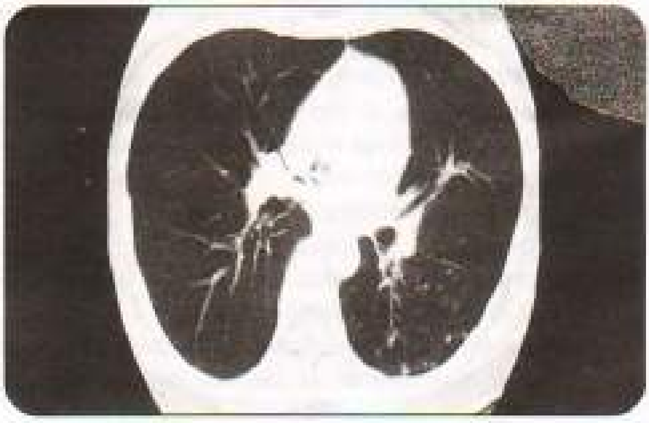


Figure 10.23: CT scan showing enlarged lymph nodes in neck.

Tuberculosis during pregnancy and in newborn

- Pulmonary and extra-pulmonary tuberculosis during pregnancy is associated with increased risk for:
    - Prematurity
    - Fetal growth retardation
    - Low birthweight
    - Perinatal mortality
- Congenital transmission usually occurs from a lesion in the placenta. Tubercle bacilli infect the fetal liver. Organisms pass through the liver into the main fetal circulation and infect many organs.
- Congenital tuberculosis can be caused by aspiration or ingestion of infected amniotic fluid.
- The most common route of tuberculosis infection in a neonate is postnatal airborne transmission from mother or an adult with infectious pulmonary tuberculosis.

Perinatal tuberculosis

- Symptoms of congenital tuberculosis may present any time between birth to one month of age. Most common clinical findings are respiratory distress, fever, hepatic or splenic enlargement, poor feeding, lethargy or irritability, lymphadenopathy, abdominal distention, failure to thrive, ear drainage, and skin lesions.
- Infant's tuberculin skin test (TST) is negative initially but can become positive within 1–3 months of age.
- A positive acid-fast stain of an early morning gastric aspirate from a newborn usually helps to diagnose tuberculosis.
- If diagnosis is delayed, mortality rate of congenital tuberculosis is very high.
- If the mother is the contact, there is no need to separate the baby and she should continue feeding the baby. In such a case, the infant should have baseline chest radiography. He should be given isoniazid (10–15 mg/kg/day). Isoniazid is continued for 3 months and then a Mantoux tuberculin test is performed. If the test is positive, anti-tuberculous treatment is continued. If the test is negative, isoniazid is discontinued and BCG vaccination is given.
- If the mother or other family members have old cases of treated tuberculosis, there will be no risk to the infant and the treatment need not be given. In such a case, tuberculin skin test is performed at 4–6 month intervals during the first year of life.

Diagnosis

- Following points are evaluated to diagnose a suspected case of tuberculosis:
    - Contact tracing
    - Tuberculin skin test
    - Interferon-γ release assays
    - Radiological diagnosis
    - AFB smear and culture of body secretions
    - Biopsy

Contact tracing

- Any adult who had Anti-Tuberculosis Therapy (ATT) within the last 2 years from a recognized institution is considered as a contact.
- This contact may be in the family (intrafamilial) or from the persons in the neighborhood who handles the child frequently (extrafamilial).

Tuberculin skin test

- Tuberculin sensitivity develops 3 weeks to 3 months after inhalation of organisms.
- It detects the presence of delayed hypersensitivity to the antigens of *M. tuberculosis*. Intra-dermal injection of tuberculin stimulates the delayed hypersensitivity, which reaches maximum in 72 hours.
- One unit of purified protein derivative is injected intracutaneously in the left forearm so as to form a wheal of about 5 mm by a sterile tuberculin syringe and a 26 guage needle. Test is seen after 48–72 hours.
- Positive response consists of a central area of induration of 10 mm and above. This induration results from migration of activated lymphocytes and macrophages.
- Negative response consists of induration of less than 5 mm.
- Induration between 5 and 10 mm is doubtful response and may be due to infection with atypical mycobacteria or prior BCG vaccination. In such conditions, the test may be repeated but on the other forearm to prevent the booster response.
- Induration >15 mm is positive in all patients even after recent inoculation of BCG.
- A negative test does not rule out tuberculosis, but a positive test is a strong evidence of active, a quiescent or past tuberculous infection.
- A positive Mantoux shows the antigenic response indicating the tuberculous infection and not about the disease.

Conditions in which mantoux test is positive

- If BCG has been given.
- Patient is suffering from active tuberculosis.
- Patient has suffered from tuberculosis in the past.
- Patient had subclinical disease and has become immune.
- Patient having repeated tuberculin tests.

Conditions in which mantoux test is negative

True negative

- Patient is not suffering from T.B.
- Patient has not been vaccinated against BCG.

False Negative

- Malnourished and debilitated patients
- Patients with miliary tuberculosis
- Patients suffering from measles or whooping cough
- Patients having steroid therapy
- Patients on cytotoxic drugs
- Patient has contacted T.B. but of less than 6 weeks duration (Incubation phase)
- Patient having immune deficiency diseases
- Faulty technique

Interferon-release assays

- Blood tests can detect IFN-γ generation by the patient's T cells in response to specific *M. tuberculosis* antigens.
- This test has higher specificity compared with the TST and fewer false-positive results.
- Like the TST (tuberculin skin test), this test cannot differentiate between tuberculosis infection and disease.

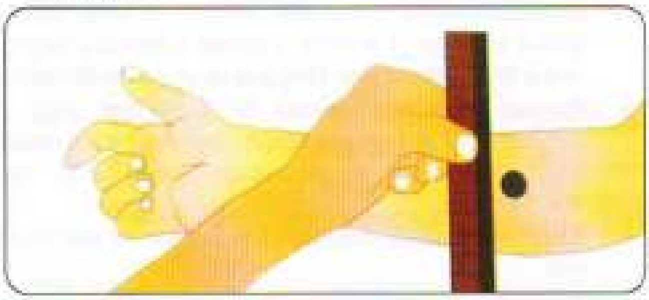


Figure 10.24: Tuberculosis skin test.

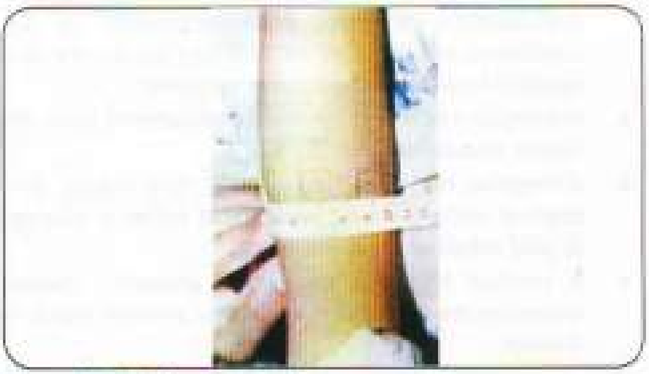


Figure 10.25: Mantoux test.

Radiological diagnosis

- As lung is the most common and the first site of involvement of tuberculosis, the diagnosis of childhood primary tuberculosis mainly rests on the X-ray evaluation of the chest.
- Primary complex in the lungs can be diagnosed by primary focus (round or coin shadow), draining lymph vessels and the hilar nodes.
- Other significant findings are:
    - Obstructive emphysema due to incomplete bronchial obstruction by enlarged lymph nodes (ball valve mechanism).
    - Tuberculous bronchopneumonia or consolidation due to aspiration of caseous material into the lung.
    - Collapse consolidation due to complete obstruction by an enlarging lymph node with absorption of air.
    - Bronchiectasis occurs if the above complications are not managed.

AFB smear and culture

- The most specific confirmation of pulmonary tuberculosis is isolation of *M. tuberculosis* from a clinical sample.

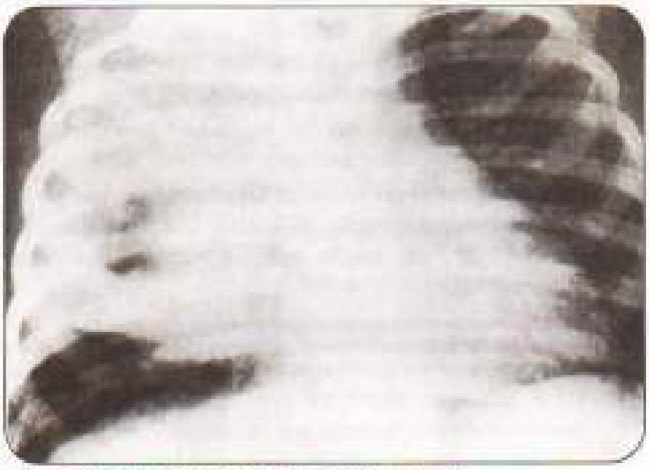


Figure 10.26: Consolidation in tuberculosis.

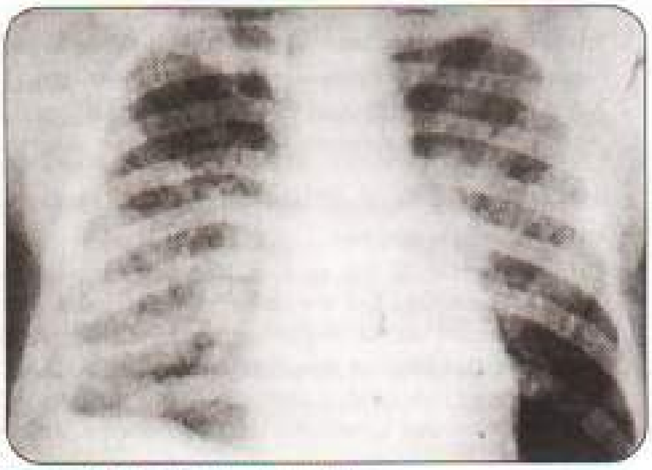


Figure 10.27: Miliary tuberculosis.

- A case of pulmonary TB is considered to be smear-positive if one or more sputum smear specimens at the start of treatment are positive for AFB. Smear-positive cases are the most infectious and most likely to transmit their disease in their surroundings.
- It is usually very difficult to get sputum in children less than 6 years of age as they swallow but not cough out the sputum.
- In young children, early morning gastric aspirate (through naso-gastric tube) is used instead of sputum. Gastric aspirates yield the organisms in 30–40% of the cases.
- Loewenstein–Jensen (LJ) media requires 4–6 weeks for isolation of the organisms and another 2–4 weeks for susceptibility testing.
- In Bactec radiometric system, culture and sensitivity results are obtained within 7–10 days and is more sensitive than the other media used for sputum cultures.

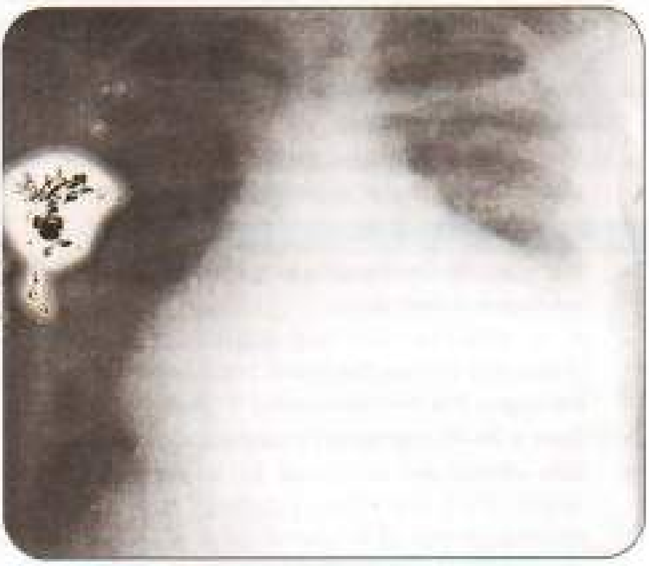


Figure 10.28: Pericarditis in tuberculosis.

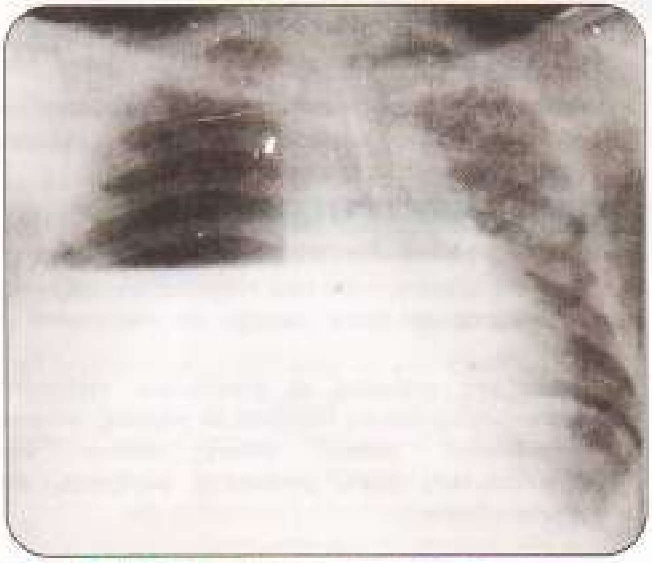


Figure 10.29: Tuberculous pyopneumothorax.

Biopsy

- In a case of tuberculous adenitis, histologic confirmation of tuberculosis requires excisional biopsy.
- Biopsy of the pleural membrane may yield a positive acid-fast stain or culture.

Other new techniques

DNA probes

- These probes use DNA sequence that is complementary to specific RNA or DNA sequence of *M. tuberculosis*.
- It is 100% sensitive and specific when used on isolated organisms; the sensitivity drops when probes are used directly on patient samples.

PCR (polymerase chain reaction)

- PCR increases the sensitivity of DNA testing. DNA of the organism is isolated and replicated thousands of times and then detected using a nucleic acid probe or specially stained electrophoresis gels.
- Results are available with PCR technique within 48 hours. It is 95% sensitive and specific for *M. tuberculosis* in sputum positive pulmonary tuberculosis.

Management

- In general, the treatment for most forms of extra-pulmonary tuberculosis, cervical tuberculous lymphadenopathy and pulmonary tuberculosis is same and is recommended for 6 months. .
- Bone and joint tuberculosis, disseminated tuberculosis, and CNS tuberculosis are treated for 9–12 months.
- Adjunct medical therapy includes surgical débridement in bone and joint disease and ventriculoperitoneal shunting in CNS disease.
- Indications for hospitalization are:
  - Tuberculous meningitis
  - Extensive pulmonary, osseous, renal or miliary tuberculosis
  - Tuberculosis in a young infant
  - For surgical intervention or steroid therapy

Specific measures

- Isoniazid and rifampicin are the two outstanding primary drugs.
- Anti-TB drugs must always be given in combinations.
- Drugs should be prescribed in correct dosages.
- Anti-TB drugs should be taken for defined duration.
- Irregular treatment leads to resistance. The Directly Observed Treatment (DOT) is the best option to ensure regular intake of anti-TB drugs. Directly Observed Treatment (DOT) means that a regular supervision is required to ensure that the patient takes all the drugs prescribed.
- During the initial intensive phase a combination of four drugs (Isoniazid, Rifampicin, Pyrazinamide and

Ethambutol are administered under observation daily for a period of two months.

- During the continuation phase, isoniazid and rifampicin (HR) are administered daily for four months.
- Prolonging chemotherapy beyond the recommended period of 6 months has minimal benefits provided the patient has taken the medication without interruption.
- Chemotherapy may need to be temporarily suspended or stopped in case of severe drug intolerance or toxicity.

Isoniazid (INH)

- It is rapidly absorbed and penetrates readily into all tissues and body fluids including CSF.
- Concentrations in the CSF are 50–100% of the plasma concentrations. Low concentrations are present in breast milk. Isoniazid is metabolized in the liver by acetylation. It is excreted primarily through the kidney. It is a well-tolerated drug.
- Transient elevation of hepatic enzymes may be present in 10% of patients. Overt clinical hepatitis occurs in only 1% of the patients. Routine monitoring of LFTs is not necessary unless there is a history of liver disease or clinical signs or symptoms of drug toxicity. Hepatic toxicity is more likely to occur if the dose of isoniazid is more than 10 mg/kg/day and rifampicin is also given with the isoniazid.
- It is bactericidal. Dose is 10–15 mg/kg/day (maximum daily dose 300 mg). Twice a week dose is 20–30 mg/kg/dose (maximum twice a week dose 900 mg.
- Hepatotoxicity and peripheral neuritis are the main side effects but hypersensitivity reactions (fever, rash, eczema) may occur.
- When isoniazid in a dosage exceeding 10 mg/kg per day is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.
- There is no need to give pyridoxine until diet is inadequate. However, breast-fed infants receiving isoniazid should always be given pyridoxine because of the low concentration of pyridoxine in breast milk.

Rifampicin

- It is well absorbed from the GIT and penetrates all body tissues and fluids, achieving CSF concentrations of 60–90% of plasma levels.
- It should be given 1 hour before or 2 hours after meal as food inhibits its absorption.
- It is metabolized in the liver and excreted in the urine.
- Dose is 10–20 mg/kg/day (maximum 600 mg). Twice daily dose is 10–20 mg/kg/dose. It is usually well-tolerated drug.
- It may color urine, sweat, tears, and feces red. Main side effect is hepatotoxicity (jaundice). Hepatic toxicity is rare (<1%) unless rifampicin is used along with isoniazid more than 10 mg/kg/day.
- Other side effects are vomiting, influenza-like reaction, thrombocytopenia, pruritus.

Pyrazinamide

- Pyrazinamide is a bactericidal drug given along with rifampicin and isoniazid for the first 2–3 months.
- Dose is 30–40 mg/kg orally/day. Twice a week dose is 50 mg/kg/dose. Maximum dose is 2 g.
- It achieves CSF levels 50–75% of plasma levels. It is active only at a pH of about 5.5 (pH inside macrophages). It is metabolized in the liver causing hepatotoxicity if dose more than 40 mg/kg/day is given.
- Other side effect are hyperuricemia (pyrazinamide inhibits urinary excretion of uric acid), arthralgia or arthritis (in 10% of cases), gout, gastrointestinal upset, and skin rash.

Ethambutol

- It is highly effective and cheap replacing pyrazinamide but poorly penetrates CSF.
- It is contraindicated in children below 6 years of age because of inability to assess color vision (visual acuity). It is usually used in re-treatment of INH resistant cases.
- Dose is 20 mg/kg/day (maximum 2.5 g). Twice a week dose is 50 mg/kg/dose.
- Side effects include optic neuritis, red-green color discrimination, hypersensitivity and GIT upset.

Streptomycin

- It is given intramuscularly as a third drug for miliary or meningeal tuberculosis.
- It is effective for drug-resistant tuberculosis. It reasonably crosses the blood brain barrier of inflamed meninges. It is excreted mainly through the kidneys.
- Dose is 20–40 mg/kg/day (maximum. 600 mg).
- Side effects are minimized by a short course of 4 weeks. Main side effect is damage to vestibular and cochlear portion of 8th cranial nerve. Other side effects are vertigo, ataxia, hearing loss, and hepatotoxicity.

Second-line drugs

- Second-line drugs are used if drug resistance to first-line drugs or toxicity becomes a problem.
- Aminoglycosides such as kanamycin and amikacin are active against most strains of M. tuberculosis including those resistant to streptomycin.

Corticosteroids

- These are beneficial in certain types of tuberculosis.
- They are effective if the host inflammatory reaction is contributing to tissue damage or impairment of function.
- These are indicated in tuberculous meningitis, endobronchial disease (localized air trapping, collapse-consolidation lesion), miliary disease with alveolocapillary block, pericarditis, peritonitis, and pleural effusion.

- Prednisolone is usually given at a dose of 1–2 mg/kg/day for 4–6 weeks with gradual withdrawal over several weeks.

General measures

- Bed rest in seriously ill children.
- Nutritious diet and physiotherapy.
- Drugs should be given in combination as double or triple therapy as a single daily dose to achieve peak levels with bactericidal activity as organisms take minimum 48 hours to divide. Patient becomes non-infectious from 9 days onward but therapy should be continued for 9–18 months.
- Children receiving anti-tuberculous treatment should be given a proper follow up to monitor the compliance and monitor the toxic reactions to medicines.

Treatment failure

- A sputum smear positive patient who remains sputum positive or after 5 months treatment.
- Also a patient who was initially smear negative before starting treatment and became smear positive after completing the initial phase of treatment.

Management of close contacts

Adult

- Screening: Chest symptoms (Cough >2 weeks or other TB symptoms)
- Action: Do sputum smears

Child with no symptoms

- Reassure
- Give BCG if not already given
- Prescribe INH in a dosage of 5 mg/kg body weight for a period of six months if age of child contact is 5 years or below.

Child with symptoms

- Refer to specialist.

Child breast fed by smear-positive mother

- Treat the mother.
- Protect the child with INH 5 mg./kg. for 6 months.
- Continue breastfeeding.
- At completion of 6 months, give BCG, if not already given.

Prevention

- Primary prevention (BCG vaccination) prevents the establishment of the tuberculous infection.
- Secondary prevention (isoniazid therapy) prevents the development of active disease after infection has occurred.

BCG vaccination

- BCG vaccine activates host cell-mediated immunity to mycobacterial antigens and prevents infection or progression to disease if a subsequent infection with *M. tuberculosis* occurs.
- Usual local reaction to an intradermal BCG vaccination is a papule that ulcerates and develops into a permanent scar in 2 months' time.
- Efficacy of BCG in preventing subsequent tuberculosis ranges from 0–80%. Most important effect of BCG is to limit serious disseminated tuberculosis especially miliary tuberculosis and meningitis.
- In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants (WHO).
- In children who are known to be HIV-infected, BCG vaccine should not be given (WHO).

Preventive therapy with isoniazid

- Isoniazid preventive therapy is indicated in:
    - Children with a positive tuberculin test but with no clinical or radiographic evidence of tuberculosis.
    - Children with a negative tuberculin test who have known recent exposure to an adult with contagious tuberculosis.
    - Children of any age who show recent conversion of the tuberculin skin test after exposure to a contagious case.
- A 1-year course of isoniazid preventive therapy is of proven efficacy.

RHEUMATIC FEVER

CASE

An 8-year-old boy presents with involuntary movements of his limbs (***chorea***). There is also history of fever, ***sore throat*** and joint pain (***migratory arthritis***). On examination, he is a pale, afebrile, breathless child with normal pulses, a marked precordial heave and displaced apex. There is a loud gallop, and a systolic murmur at the apex radiating to the axilla (***carditis***).

- Rheumatic fever is delayed, non-suppurative sequelae to upper respiratory infection with Group AB-hemolytic Streptococci (GAS).

Epidemiology/etiology

- Annual incidence is 50 per 100,000 children.
- There are many factors predisposing to rheumatic fever. These include the age of the patient, family history, season, recurrent streptococcal infections, and host factors affecting susceptibility.
- First attack of the rheumatic fever usually occurs in children between 5–15 years of age. Rheumatic fever is rare in children less than 4 years of age. There is no sex preference except in case of chorea in which the incidence is slightly greater in girls.
- Incidence of rheumatic fever is decreasing in our country.
- Rheumatic fever relates to poverty, overcrowding, poor housing and inadequate health services. High

temperatures of the tropics also favor the spread of pharyngeal streptococci. There are more chances of streptococcal pharyngitis in these seasons.

- Once rheumatic fever is acquired, its reactivation after subsequent streptococcal infections is more likely. Recurrence rate is about 50% during the first year after the initial attack. After that, it decreases. After several years, the recurrence rate decreases to 10%.
- About 1–5% rheumatogenic strains of streptococcal throat infections lead to rheumatic fever.
- Skin infections are unlikely to produce rheumatic fever.

Pathogenesis

- The cytotoxic theory suggests that GAS toxin such as streptolysin O, has cytotoxin effect on cardiac cells but does not explain the latent period of 2–4 weeks.
- An immune-mediated pathogenesis suggest cross-reactivity between GAS epitopes and cardiac antigen epitopes. The common epitopes are shared between certain GAS component (e.g; M protein, group A cell wall carbohydrate, capsular hyaluronate) and human heart valve brain, joint and sarcomere.

Clinical findings

- The interval between the onset of pharyngitis and the symptoms of rheumatic fever is 1–5 weeks (average 3 weeks). In some cases, history of a preceding streptococcal infection may not be present.
- The clinical findings vary greatly and are determined by the site of involvement, severity of attack and the stage at which patient is first examined.
- Onset is acute when arthritis is the presenting symptom while gradual when carditis or chorea is the initial clinical feature.
- High intermittent fever and sweating is a striking feature of this disease but often patient is afebrile and polyarthritis may be seen no more than aches and pains of almost any febrile illness. In this, child fails to recover after a cold or sore throat, becomes listless, loses weight, gets easily fatigued but has relatively minor complaints of limb pain.
- There are **5 major**and **4 minorcriteria**and a requirement of evidence of recent GAS infection.

Duckett–Jones criteria (revised) for the diagnosis of rheumatic fever

- The diagnosis of acute rheumatic fever is essentially clinical.
- Two major manifestations or one major and two minor manifestations plus evidence of a preceding streptococcal infection indicate a high likelihood of rheumatic fever.
- Carditis is now defined as clinical and/or subclinical (echocardiographic valvulitis).

Table 10.16: Duckett Jones Criteria for the diagnosis of rheumatic fever (2015).

Major Manifestations
• Carditis • Polyarthritis, migratory • Erythema marginatum • Chorea • Subcutaneous nodules
Minor Manifestations
• **Clinical features:** • Fever • Arthralgia • **Laboratory features:** • Elevated acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein) • Prolonged PR interval on an electrocardiogram
Supporting evidence of antecedent group A streptococcal infection
• Positive throat culture or rapid streptococcal antigen test • Elevated or increasing streptococcal antibody titer.

- There are three special circumstances where the diagnosis of rheumatic fever is acceptable without two major or one major and two minor criteria. Only for 1 and 2 given below can the requirement for evidence of a preceding streptococcal infection be ignored.
  1. Chorea, if the other causes of chorea have been excluded.
  2. Insidious or late-onset carditis with no other explanation.
  3. Rheumatic recurrence: In patients with documented rheumatic heart disease or previous rheumatic fever, the presence of one major criteria or of fever, arthralgia, or elevated acute-phase reactants is suggestive of a presumptive diagnosis of recurrence. Here, the evidence of previous streptococcal infection is needed.

Migratory polyarthritis

- Arthritis occurs in approximately 75% of patients with acute rheumatic fever.
- The arthritis of rheumatic fever is an acute painful swelling of one of several joints.
- It is migratory in character i.e. the first affected joint starts improving while another becomes affected.
- Larger joints, such as knee, ankle, wrist, elbow and shoulder (in order of frequency) are involved.
- The joints are hot, red, swollen and very tender and the child is unable to move the affected limb.
- After recovery, however, there is no residual damage.
- Arthritis responds almost immediately to salicylates.

- Severity of joint involvement is inversely proportional to the severity of cardiac involvement.

Carditis

- It presents as palpitation, chest pain or breathlessness.
- Carditis occurs in approximately 50–60% of all cases of acute rheumatic fever. Recurrent attacks of acute rheumatic fever in patients who had carditis with their initial attack are associated with high rates of carditis with increasing severity of cardiac disease. The major consequence of acute rheumatic carditis is chronic, progressive valvular disease, particularly valvular stenosis, which can require valve replacement.
- A major change in the 2015 revision of the Jones Criteria is the acceptance of subclinical carditis (defined as without a murmur of valvulitis but with echocardiographic evidence of valvulitis) or clinical carditis (with a valvulitis murmur) as fulfilling the major criterion of carditis in all populations.
- There may be a soft mid-diastolic murmur (Carey-Coombs murmur) due to the nodules forming on the mitral valve leaflets.
- A mid-diastolic murmur over the apex is a definite sign of mitral valvulitis. It is caused by narrowing of the mitral valve by the thickened and edematous cusps.
- In aortic valvulitis, there is a high-pitched, early-diastolic murmur over the base.
- There may be pericardial friction rub or congestive cardiac failure may occur from myocarditis or aortic or mitral valve incompetence.
- In chronic rheumatic heart disease the valves involved in order of frequency are mitral, aortic and tricuspid valve. Initially there is mitral incompetence followed by stenosis in 2–10 years. Once the signs of activity of acute rheumatic fever has subsided but signs of residual valvular damage are present then it is called rheumatic heart disease.
- Carditis is suspected if there is:
  - High sleeping pulse rate
  - Cardiomegaly
  - Soft or muffled 1st heart sound
  - A diastolic apical murmur or changing character of murmur
  - Pericardial friction rub

Rheumatic or sydenham's chorea

- Sydenham chorea occurs in approximately 10–15% of patients with acute rheumatic fever.
- It is a late manifestation of rheumatic fever.
- It is more common in girls and may occur up to 6 months after initial streptococcal infection.
- Chorea is never seen simultaneously with arthritis. It may coexist with carditis.
- It is characterized by jerky, involuntary purposeless movements, which are non-repetitive, and mainly in the proximal limb muscles or trunk.
- Gait is irregular and there is deterioration in speech and handwriting.
- There is hypotonia and emotional disturbances with abrupt alterations between laughter and tears.
- In the outstretched hands, there is flexion at the wrist and dorsiflexion of the fingers.
- It is self-limiting and may last from 1 week to more than 2 years.
- Although the acute illness is distressing, chorea rarely leads to permanent neurologic sequelae.

Erythema marginatum

- Erythema marginatum is present in approximately 1% of patients with acute rheumatic fever. It is a characteristic rash of acute rheumatic fever.
- Skin lesions are serpiginous in pattern.
- They start as raised red macules with pale center and are evanescent in character (the margins progress as the center clears).
- The raised red margins may coalesce or overlap.
- The rash occurs mainly over the trunk and the proximal parts of the limbs.

Subcutaneous nodules

- Subcutaneous nodules are present in ≤1% of patients with acute rheumatic fever and consist of firm nodules approximately 1 cm in diameter.
- Subcutaneous nodules usually indicate severe carditis.
- These occur on the extensor surface and bony prominences of the arms and legs and also on the scapula and mastoid processes.

Diagnosis

- Diagnosis of rheumatic fever is very important because by long-term anti-streptococcal therapy, serious cardiac disease can be prevented or minimized.

ESR

- Although non-specific it is raised in acute stage and is useful index for monitoring activity and progress of the disease.
- It is also raised in anemia but falls in congestive heart failure.

C-reactive protein

- It is also non-specific acute phase reactant and raised in acute stage of the disease.
- It is not influenced by anemia.

Antistreptolysin O (ASO) titer

- Acute rheumatic fever typically develops 2–4 weeks after an acute episode of group A streptococcal (GAS) pharyngitis.
- At this time, there may be no clinical findings of pharyngitis or only 10–20% of patients still have GAS in the throat.
- One-third of patients with acute rheumatic fever have no history of an antecedent pharyngitis.

- Therefore, evidence of an antecedent GAS infection is usually based on elevated or rising serum antistreptococcal antibody titers.
- It is an essential criteria in diagnosis and is raised in 85% of patients.
- It indicates recent streptococcal infection. It is always above 200 Todd units per ml and remains elevated for weeks or months. A single value of 500 units indicates recent streptococcal infection. A value of 333 units has a borderline significance. If the ASO titer is 333 units or less, it is recommended that additional anti-streptococcal antibody assay should be obtained.
- ASO and anti-DNase are commonly used for diagnosis. Anti-hyaluronidase is the third choice to be measured.

Throat swab culture

- More direct evidence of streptococcal infection can often be obtained by culture of throat swab as infection may still be present in the throat if antibiotics have not been given.

Blood

- Hemoglobin is reduced (anemia) during the acute phase and there is polymorphonuclear leucocytoses.

ECG

- The earliest feature of myocarditis is prolongation of the PR interval to greater than 0.18 second.
- There is also prolongation of the QT interval.
- Second-degree or a complete AV block may occur in response to inflammation of the conduction system.
- ST wave and T wave changes of pericarditis or myocarditis may be present.

X-ray chest

- A chest X-ray may reveal cardiac enlargement due to congestive cardiac failure or pericarditis.

Echocardiography

- Changes can detect valvular and myocardial involvement or pericardial effusion.
- Echocardiography is helpful in monitoring valve problems and allows an estimate to be made of its severity and need for valve replacement.

Differential diagnosis

Arthritis

- Juvenile idiopathic arthritis
- Reactive arthritis (e.g. *Shigella, Salmonella, Yersinia*)
- Malignancy
- Sickle cell disease
- Systemic lupus erythematosis
- Pyogenic arthritis
- Poststreptococcal reactive arthritis

Carditis

- Innocent murmur
- Viral myocarditis
- Viral pericarditis
- Infective endocarditis
- Kawasaki disease
- Congenital heart disease
- Mitral valve prolapsed

Chorea

- Huntington chorea
- Wilson's disease
- Cerebral palsy
- Hyperactivity
- Tic disorder

Management

Bed rest

- It is desirable in patients who have carditis or arthritis until all signs and symptoms of acute inflammation disappear, i.e. heart rate and temperature becomes normal. The ESR is more specific for activity.
- Bed rest is recommended for 1–2 weeks in cases of arthritis alone, 2–4 weeks with minimal carditis and several months with moderate to severe carditis.
- Salt is restricted if signs of heart failure are observed.

Antibiotic therapy

- The eradication of streptococci is an essential part of treatment and organisms may still be present in pharyngeal tissue or tonsils even when throat cultures are negative.
- Drug of choice is benzyl penicillin.
- One IM injection of benzathine penicillin 6–12 lac units or a 10 days course of oral penicillin G 500–1000 mg four times a day or amoxicillin is given.
- Patients, who are allergic to penicillin, should receive azithromycin (5 days), erythromycin (250–500 mg, four times daily) for 10 days or clindamycin.

Anti-inflammatory drugs

- Salicylates (aspirin) and corticosteroids are valuable drugs for symptomatic relief, but they are not curative and may prolong the course of the disease.
- Aspirin:
    - Patients with typical migratory polyarthritis and those with carditis without cardiomegaly or congestive heart failure should be treated with oral salicylates.
    - The usual dose of aspirin is 50–70 mg/kg/day in four divided doses PO for 3–5 days, followed by 50 mg/kg/day in four divided doses PO for 3 weeks and half that dose for another 2–4 weeks.
    - There is no evidence that nonsteroidal anti-inflammatory agents are any more effective than salicylates.
    - If dose is too much then signs of salicylism will develop i.e. vomiting, tinnitus, gastric irritation, bleeding due to inhibition of platelet function, metabolic acidosis, hyperventilation leading to respiratory alkalosis, and hypoglycemia; in such a

    case the drug is withdrawn or dose further reduced. Aspirin is also given to patients with or without mild carditis, if there are side effects or contraindications to corticosteroids, and during and after withdrawal from corticosteroids.

- Corticosteroids:
    - Corticosteroids are recommended in children with carditis and more than minimal cardiomegaly and/or congestive heart failure.
    - Prednisolone is 2 mg/kg/day in four divided doses is given for 2–3 weeks followed by half the dose for 2–3 weeks and then tapering of the dose by 5 mg/24 hours every 2–3 days.
    - When prednisolone is tapered, aspirin should be started at 50 mg/kg/day in four divided doses for 6 weeks to prevent rebound of inflammation.
    - Prednisolone is reserved for those patients with moderate to severe carditis but it does not markedly shorten the course of illness or diminish the occurrence of cardiac damage.
    - It has a dramatic effect in relieving fever, arthritis, subcutaneous nodules, erythema marginatum, and bringing ESR to normal.
    - Corticosteroids are seldom indicated for the treatment of arthritis or rheumatic fever.

Treatment of Sydenham chorea

- Chorea often occurs as an isolated manifestation after the resolution of the acute phase of the disease.
- Anti-inflammatory agents are usually not indicated.
- Sedatives are indicated early in the course of chorea:
    - Phenobarbital (16–32 mg every 6–8 hours PO) is the drug of choice.
    - If phenobarbital is ineffective, then haloperidol (0.01–0.03 mg/kg/24 hours divided bid PO) or chlorpromazine (0.5 mg/kg every 4–6 hours PO) should be initiated.
- Some patients may benefit from corticosteroids for a few weeks.
- Patients with chorea should remain in a quite atmosphere and protected from self-injury.

Treatment of heart failure

- Heart failure may be an indication for the use of steroids, diuretic agents, or digoxin. For patients with mild carditis without evidence of congestive heart failure, salicylates alone are indicated. In patients with congestive heart failure or other manifestations of carditis, corticosteroids are indicated.
- If the signs and symptoms of severe congestive failure are unresponsive to medical therapy, operative repair or replacement of a severely compromised cardiac valve may be necessary.

Complications

- Arthritis and chorea of acute rheumatic fever resolve completely without sequelae.
- Long-term sequelae of rheumatic fever are related to heart.

Prognosis

- Prognosis depends on:
    - Clinical manifestations present at the time of the initial episode
    - Severity of the initial episode
    - Presence of recurrences
- The risk of residual heart disease is greater if the initial cardiac involvement is more severe.
- Approximately 50–70% of patients with minimal carditis recover with no residual heart disease.
- Cardiac involvement increases with increasing number of recurrent rheumatic fever attacks.
- Patients with carditis during the initial episode are very likely to have carditis with recurrences.
- Risk for permanent heart damage increases with each recurrence.
- Continuous chemoprophylaxis against GAS pharyngitis is needed for patients who have rheumatic fever to prevent recurrence (approximately 50% risk of recurrence with each GAS pharyngitis).

Prevention

- Prevention of both initial and recurrent episodes of acute rheumatic fever is achieved by controlling GAS infections of the upper respiratory tract.
- Prevention of initial attacks is called primary prevention. It depends on eradication of GAS causing acute pharyngitis.
- Children with previous acute rheumatic fever attack are particularly susceptible to recurrences of rheumatic fever with any subsequent GAS upper respiratory tract infection.
- Such patients require secondary prevention with continuous antibiotic prophylaxis to prevent recurrences.

Primary prevention

- Appropriate antibiotic therapy started before the 9th day of symptoms of acute GAS pharyngitis is effective to prevent in preventing first attacks of acute rheumatic fever.

Secondary prevention

- A single IM injection of 6–12 lac of benzathine penicillin is the most effective method (compliance is assured).
- Oral penicillin prophylaxis is given by 500–1000 mg of penicillin given twice daily.
- In case of allergy to the penicillin, erythromycin 250 mg is given twice daily. Sulphadiazine may also be given to patients who are allergic to penicillin. The dose of sulphadiazine is 0.5 gm/day below 30 kg and 1.0 gm/day above 30 kg weight. Alternative are clarithromycin or azithromycin.

Table 10.17: Duration of prophylaxis for patients who have had acute rheumatic fever.

Category	Duration
Rheumatic fever without carditis	5 yrs or until 21 yrs of age, whichever is longer
Rheumatic fever with carditis but without residual heart disease (no valvular disease*)	10 yrs or until 21 yrs of age, whichever is longer
Rheumatic fever with carditis and residual heart disease (persistent valvular disease*)	10 yrs or until 40 yrs of age, whichever is longer; sometimes lifelong prophylaxis

* Clinical or echocardiographic evidence.

DENGUE FEVER

CASE

A 4-year-old boy presents with ***fever*** and ***rash*** for one day. Rash is rapidly spreading over the body. There is ***bleeding*** from the mouth. He is drowsy for the last 6 hours. On examination, he has cold extremities and temperature 103°F. There is wide spread purpuric and petechial rash on upper and lower extremities. Platelet count is 50,000/mm^3 (***thrombocytopenia***).

- Dengue is a mosquito-borne infection, which in recent years has become a major international public health concern.
- Dengue is found in tropical and sub-tropical regions around the world, predominantly in urban and semi-urban areas.
- There are at least 4 distinct antigenic types of dengue virus (dengue 1,2, 3, and 4), members of the family Flaviviridae.

Dengue hemorrhagic fever

- Dengue Hemorrhagic Fever (DHF), a potentially lethal complication, has become a leading cause of hospitalization and death among children.
- As there are four distinct, but closely related, viruses that cause dengue, recovery from infection by one provides lifelong immunity against that serotype but confers only partial and transient protection against subsequent infection by the other three.
- Dengue hemorrhagic fever occurs where multiple types of dengue virus are simultaneously or sequentially transmitted. It is characterized by:
- Capillary permeability.
- Abnormalities of hemostasis.
- A protein-losing shock syndrome (dengue shock syndrome).
- Sequential infection increases the risk of more serious disease resulting in DHF.

Transmission

- Dengue viruses are transmitted to humans through the bites of infective female *Aedesaegypti* mosquitoes (a daytime biting mosquito).
- In most tropical areas, *A. aegypti* has breeding sites in water stored for drinking or bathing and in rainwater collected in any container.
- Mosquitoes generally acquire the virus while feeding on the blood of an infected person. After virus incubation for 8–10 days, an infected mosquito is capable, during probing and blood feeding, of transmitting the virus, to susceptible individuals for the rest of its life. Infected female mosquitoes may also transmit the virus to their offspring by transovarial (via the eggs) transmission.
- Humans are the main amplifying host of the virus. The virus circulates in the blood of infected humans for two to seven days, at approximately the same time as they have fever; *Aedes* mosquitoes may acquire the virus when they feed on an individual during this period.

Clinical findings

- Dengue fever is a severe, flu-like illness that affects infants, young children and adults.
- The incubation period is 1–7 days.
- The clinical features of dengue fever vary according to the age of the patient. Infants and young children may have a non-specific febrile illness with rash. Older children and adults may have either a mild febrile syndrome or the classical incapacitating disease with abrupt onset and high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash.
- Dengue hemorrhagic fever is a potentially deadly complication that is characterized by high fever, hemorrhagic phenomena-often with enlargement of the liver-and in severe cases, circulatory failure. The illness commonly begins with a sudden rise in temperature accompanied by facial flush and other non-specific constitutional symptoms of dengue fever. The fever usually continues for two to seven days and can be as high as 40–41°C, possibly with febrile convulsions and hemorrhagic phenomena. In moderate DHF cases, all signs and symptoms abate after the fever subsides. In severe cases, the patient's condition may suddenly deteriorate after a few days of fever; the temperature drops, followed by signs of circulatory failure, and the patient may rapidly go into a critical state of shock and die within 12–24 hours, or quickly recover following appropriate volume replacement therapy.

Diagnosis

- A clinical diagnosis of dengue fever depends on a high index of suspicion in an area where dengue fever is common.

- Confirmed by isolation of the virus, viral antigen, or genome by polymerase chain reaction analysis.
- There is a four-fold or greater increase in antibody titers.
- The most common hematologic abnormalities are hemoconcentration with an:
  - Increase of >20% in hematocrit
  - Thrombocytopenia
  - Prolonged bleeding time
  - Moderately decreased prothrombin level that is seldom <40% of control
  - Fibrinogen levels may be subnormal
  - Fibrin split-product values are elevated
- Radiograph of the chest reveal pleural effusions (right >left) in nearly all patients with dengue shock syndrome.
- Ultrasonography can be used to detect serosal effusions of the thorax or abdomen.

World Health Organization criteria for dengue hemorrhagic fever

- Fever (2–7 days in duration or biphasic)
- Minor or major hemorrhagic manifestations
- Thrombocytopenia (≤100,000/μL)
- Objective evidence of increased capillary permeability (hematocrit increased by ≥20%), pleural effusion or ascites (by chest radiography or ultrasonography), or hypoalbuminemia

Dengue shock syndrome criteria

- Dengue hemorrhagic fever
- Hypotension
- Tachycardia
- Narrow pulse pressure (≤20 mmHg)
- Signs of poor perfusion (cold extremities)

Severe dengue fever criteria

- Dengue hemorrhagic fever and dengue shock syndrome.
- Encephalitis or encephalopathy associated with dengue infection.
- Respiratory distress that may be due to pulmonary edema caused by overhydration.

Differential diagnosis

- Dengue-like diseases
- Viral respiratory and influenza-like diseases
- Early stages of malaria
- Mild yellow fever
- Scrub typhus
- Viral hepatitis
- Leptospirosis

Management

- Treatment of uncomplicated dengue fever is supportive.
- Bed rest during the febrile period.
- Antipyretics to keep body temperature <40°C (104°F).
- Analgesics or mild sedation to control pain.
- Aspirin is contraindicated because of its effects on hemostasis.
- Fluid and electrolyte replacement is required.
- Dengue shock syndrome is a medical emergency.
- Management of dengue hemorrhagic fever and dengue shock syndrome includes:
  - Immediate evaluation of vital signs and degrees of hemoconcentration, dehydration, and electrolyte imbalance.
  - Patients who are cyanotic or have labored breathing should be given oxygen.
  - Rapid intravenous replacement of fluids and electrolytes.
  - Care must be taken to avoid overhydration, which may contribute to cardiac failure.
  - Transfusions of fresh blood or platelets suspended in plasma may be required to control bleeding.
  - Salicylates are contraindicated.
  - Disseminated intravascular coagulation may require treatment.

Complications

- Hypervolemia may be life threatening
- Fluid and electrolyte losses
- Hyperpyrexia
- Febrile convulsions
- Epistaxis, petechiae, and purpuric lesions

Prognosis

- The prognosis is good for dengue fever.
- The prognosis of dengue hemorrhagic fever is adversely affected by late diagnosis and delayed or improper treatment.
- Death due to shock may occur in 40–50% of patients.
- Many deaths are caused by overhydration.

Prevention

- At present, the only method of controlling or preventing dengue and DHF is to control and eradicate the vector mosquitoes.
- *Aedes aegypti* breeds primarily in containers used for domestic water storage, as well as discarded plastic food containers, used automobile tyres and other items that collect rainwater. It also breeds sometimes in natural habitats such as tree holes and leaf axils.
- Vector control is implemented using environmental management and chemical methods. Proper solid waste disposal and improved water storage practices, including covering containers to prevent access by egg laying female mosquitoes are among methods that are encouraged through community-based programmes.
- The application of appropriate insecticides to larval habitats prevent mosquito breeding for several weeks but must be re-applied periodically.

- Small, mosquito-eating fish and copepods (tiny crustaceans) have also been used with some success.
- During outbreaks, emergency control measures may also include the application of insecticides as space sprays to kill adult mosquitoes.

LEISHMANIASIS

CASE

A 9-year-old boy presents with history of ***high grade fever for 3 months***. On examination, he is febrile (41°C), ***anemic*** with ***massive hepatosplenomegaly***. There is no jaundice, skin rash or lymphadenopathy. His Hb is 5.2 g%. TLC 2250/mm^3 and platelets 55000/mm^3. Peripheral blood smear is normal. ***Slide for MP*** is also ***negative***.

- Leishmaniasis is caused by intracellular protozoan parasites of the genus *Leishmania*.
- It is transmitted by phlebotomine sand flies.
- Leishmaniasis causes human disease involving the skin and mucosal surfaces and the visceral reticuloendothelial organs.
- Cutaneous disease is usually mild but may cause cosmetic disfigurement.
- *Leishmania* organisms that primarily cause cutaneous disease do not cause visceral disease.
- Cutaneous leishmaniasis lesion shows intense chronic granulomatous inflammation involving the epidermis and dermis.
- In visceral leishmaniasis, there is prominent reticuloendothelial cell hyperplasia in the liver, spleen, bone marrow, and lymph nodes. Leishmania amastigotes are abundant in the histiocytes and Kupffer cells.

Table 10.18: Main symptoms and signs of leishmaniasis (according to frequency) in children.

Symptoms	Signs
• Fever • Abdominal distension • Anorexia • Sweating • Pallor • Weight loss • Malaise • Cough • Vomiting • Chills	• Splenomegaly • Fever • Hepatomegaly • Edema • Jaundice • Sparse and brittle hair • Lymphadenopathy • Petechiae, pupura and ecchymosis

Clinical findings

Cutaneous leishmaniasis

- Local cutaneous leishmaniasis (oriental sore)presents as one or a few papular, nodular, plaque-like, or ulcerative lesions.
- It is usually located on exposed skin, such as the face and extremities.
- It begins as a small papule at the site of the sandfly bite.
- The lesion then enlarges to 1–3 cm in diameter and after several weeks to months may ulcerate.
- The ulcer is shallow, nontender and surrounded by a sharp, indurated, erythematous margin.
- There is no drainage.

Mucosal leishmaniasis

- Mucosal leishmaniasis (espundia) is infection resulting from hematogenous metastases to the nasal or oropharyngeal mucosa from a cutaneous infection.
- There may be nasal congestion, discharge, and recurrent epistaxis.

Visceral leishmaniasis

- Visceral leishmaniasis (kala-azar) occurs after inoculation of the organism into the skin by the sandfly.
- Child may have a completely asymptomatic infection or an illness that either resolves spontaneously or evolves into kalaazar within 2–8 months.
- Classic clinical features of visceral leishmaniasis are high fever, marked splenomegaly, hepatomegaly, and severe cachexia.
- These findings develop approximately 1–6 months after the onset of the illness.
- In severe and terminal stages of kala-azar, there is massive hepatosplenomegaly, gross wasting, the profound pancytopenia, jaundice, edema, and ascites.
- Severe anemia may precipitate heart failure.
- Bleeding episodes, especially epistaxis, are present.
- Secondary bacterial infections may cause death.

Diagnosis

- The development of one or several slowly progressive, nontender, nodular, or ulcerative lesions in a patient in an endemic area should be suspected of cutaneous leishmaniasis.
- Patients with cutaneous leishmaniasis or mucosal leishmaniasis usually do not have abnormal laboratory results.
- Laboratory findings associated with classic kala-azar include:
    - Anemia (hemoglobin 5–8 gm/dL)
    - Thrombocytopenia
    - Leucopenia (2,000–3,000 cells/µL)
    - Elevated hepatic transaminase levels
    - Hyperglobulinemia (>5 g/dL) that is mostly immunoglobulin G
- Definitive diagnosis of leishmaniasis is established by the demonstration of amastigotes in tissue specimens or isolation of the organism by culture.

Differential diagnosis of visceral leishmaniasis

- Malaria
- Typhoid fever
- Miliary tuberculosis
- Schistosomiasis
- Brucellosis
- Amebic liver abscess
- Infectious mononucleosis
- Lymphoma
- Leukemia

Management

- Specific anti-leishmanial therapy is not usually needed for uncomplicated cutaneous leishmaniasis because there is spontaneous resolution in many cases.
- Cutaneous lesions which are extensive disabling, causing a cosmetic disfigurement and not healing within 3–4 months should be treated.
- All patients with visceral leishmaniasis and mucous leishmaniasis should receive therapy.
- The pentavalent antimony compounds (sodium stibogluconate) and meglumine antimoniate are the main anti-leishmanial chemotherapy.
- Dose of sodium stibogluconate is 20 mg/kg/day intravenously or intramuscularly for 20 days (for cutaneous leishmaniasis) or 28 days (for mucosal leishmaniasis and visceral leishmaniasis).
- Repeated courses of therapy may be needed in patients with severe leishmaniasis.
- Clinical response to therapy usually occurs in the 1st week of therapy.
- Adverse effects of antimony therapy are dose and duration related. These include fatigue, arthralgias and myalgias, abdominal discomfort, elevated hepatic transaminase level, elevated amylase and lipase levels, mild hematologic changes (slightly decreased leukocyte count, hemoglobin level, and platelet count), and nonspecific T-wave changes on electrocardiography.
- Amphotericin B is also used for the treatment of visceral leishmaniasis and sometimes used as first-line therapy. Amphotericin B is given at doses of 0.5–1.0 mg/kg every day or every other day for 14–20 doses. This has about 100% cure rate in visceral leishmaniasis but is nephrotoxic.
- Parenteral treatment of visceral leishmaniasis with aminoglycoside paromomycin is about 90% effective.
- Miltefosine (a membrane-activating alkylphospholipid) is treatment for visceral leishmaniasis and has a cure rate of about 80–90%. Oral dose is 50–100 mg/day (or 2.5 mg/kg for children younger than 12 years of age) for 28 days.
- Ketoconazole is also effective for cutaneous leishmaniasis.
- Fluconazole in high doses (up to 8 mg/kg/day) for 4–8 weeks is effective for cutaneous leishmaniasis.
- Topical treatment of cutaneous leishmaniasis with paromomycin ointment is effective in selected cases.

Prevention

- Avoidance of exposure to the nocturnal sandflies
- Use of insect repellent and permethrin-impregnated mosquitoes netting
- Community-based residual insecticide spraying
- Control or elimination of infected reservoir hosts (e.g. seropositive domestic dogs)
- Vaccination of humans or domestic dogs is under investigation for the control of leishmaniases in the future

RABIES

CASE

A 13-year-old boy has history of ***dog bite*** on his left arm 4 months ago for which he got no treatment. He has history of pain in his left shoulder for last many days. Now, he presents with fever, dysphagia, ***muscle spasms***, ***hallucinations*** and ***excessive salivation***.

- Rabies virus is a RNA virus from the family Rhabdoviridae.
- The classic rabies virus (genotype 1) is distributed worldwide and naturally infects a large variety of animals (mainly carnivores and bats)
- Transmission from dogs accounts for >90% of human cases.

Transmission

- Rabies virus is found in large quantities in the saliva of infected animals.
- After a bite or scratch from a rabid animal, transmission occurs through inoculation of the infected saliva.
- After bite of an rabies infected animal, about 35–50% of people contract rabies.
- Chance of transmission is increased if the victim has suffered multiple bites.
- If the inoculation of saliva occurs in highly innervated parts of the body (e.g. face and the hands).
- Infection does occur through intact mucous membranes, but does not occur through intact skin.
- Risk of rabies is assessed according to the type of animal, wound extent and location (infection more common after head or hand bites), wounds have less or extensive salivary contamination, wounds quickly and thoroughly cleaned or not, and animal vaccination history (risk low if vaccinated).

Pathogenesis

- After inoculation, rabies virus replicates slowly in muscle or skin. This is reason for long incubation period of rabies.

- Then, virus enters the peripheral motor nerves.
- Rapid dissemination occurs throughout the brain and spinal cord.
- Infection concentrates mainly in the brainstem, causing autonomic dysfunction and relative sparing of cognition.
- The pathologic hallmark of rabies is the Negri body. It is composed of clumped viral nucleocapsids that create cytoplasmic inclusions on routine histology. Negri bodies may be absent in documented rabies virus infection.

Clinical findings

- There is history of animal bite 10 days to 1 year (usually <90 days) previously.
- Incubation period of rabies is about 1–3 months.
- If there are severe wounds to the head, symptoms may occur within 5 days after exposure.
- Rabies has two main clinical forms.

Encephalitic (furious) rabies

- There are nonspecific symptoms, including fever, sore throat, malaise, headache, nausea, vomiting, and weakness.
- There is paresthesia and pruritus at or near the site of the bite which extends along the affected limb.
- Then, symptoms of encephalitis develop (agitation, depressed mentation, and, occasionally, seizures).
- Hydrophobia and aerophobia are the cardinal signs of rabies. This includes agitation by water and air. This may cause choking and aspiration through spasms of the pharynx, neck, and diaphragm.
- Death almost always occurs within 1–2 days of hospitalization.

Paralytic (dumb) rabies

- It is less frequent.
- It is characterized by fever and ascending motor weakness affecting both the limbs and the cranial nerves.

Differential diagnosis

- All forms of severe cerebral infections, infectious encephalitis
- Tetanus
- Some intoxications and envenomations
- Paralytic rabies should be differentiated from Guillain-Barré syndrome

Diagnosis

- Reverse transcription polymerase chain reaction
- Rabies virus RNA can be detected in saliva, skin, and brain by the reverse transcription polymerase chain reaction.
- Rabies antigen is detected through immunofluorescence of saliva or biopsies of hairy skin or brain.
- Rabies-specific antibody can be detected in serum or CSF samples of some but not all patients. Antirabies antibodies in serum may be present due to incomplete vaccination. Antibodies in CSF are rarely detected after vaccination and is considered diagnostic of rabies regardless of immunization status.
- MRI findings in the brain are late and are not diagnostic.

Management

- Rabies is generally fatal.
- Antiviral treatments is not been effective.
- Appearance of the normal antibody response by 7 days is associated with clearance of salivary viral load and survival.
- Early diagnosis is important for the protection and prophylaxis of individuals exposed to the patient.

Prevention

- Primary prevention of rabies infection includes:
  - Vaccination of domestic animals
  - Education to avoid wild animals, stray animals, and animals with unusual behavior

Immunization of animal reservoirs

- Routine rabies immunization for domestic pets may eliminate infection in dogs.

Post-Exposure Prophylaxis (PEP)

- If the animal is healthy and available for 10 days of observation:
  - Prophylaxis is given only if animal shows signs of rabies.
  - During the 10–day observation period, at the first sign of rabies in the biting dog or cat, treatment of the exposed person with RIG (human rabies immunoglobulin) and vaccine should be initiated.
  - The animal should be euthanized immediately and tested.
- If the animal is rabid or suspected of being rabid:
  - Immediate immunization and RIG is recommended.
  - Animal should be euthanized and tested as soon as possible.
  - Holding for observation is not recommended.
  - Immunization is discontinued if immunofluorescent test result for the animal is negative.
- If the animal status is unknown (escaped) then consult public health officials for advice.
- Vaccine and RIG are contraindicated once symptoms develop.
- First important step in rabies PEP is to cleanse the wound thoroughly. Soapy water is sufficient to inactivate virus. Other disinfectants (iodine-containing preparations) are virucidal and may be used.
- Cosmetic repair of the wound should follow.

- Antibiotics and tetanus prophylaxis should be applied.
- Second important step of rabies PEP consists of passive immunization with RIG.
    - Human Rabies Immunoglobulin (RIG) is administered at a dose of 20 IU/kg.
    - As much of the dose is infused around the wound as possible.
    - Remainder RIG is injected intramuscularly in a limb distant from the one injected with the killed vaccine.
- Third important component of rabies PEP is immunization with inactivated vaccine. Vaccine is administered intramuscularly in a 1 ml volume in the deltoid or anterolateral thigh on days 0, 3, 7, and 14 after presentation. Injection into the gluteal area is associated with a less antibody response, so not used.

Pre-exposure prophylaxis

- Killed rabies vaccine can be given to prevent rabies in persons at high risk for exposure to rabid animals.
- The schedule for pre-exposure prophylaxis consists of 3 intramuscular injections on days 0, 7, and 21 or 28.
- Post-Exposure Prophylaxis (PEP) in the patient who has received pre-exposure prophylaxis or a prior full schedule of PEP consists of 2 doses of vaccine (1 each on days 0 and 3) and does not require RIG.
- Immunity from pre-exposure prophylaxis wanes after several years and requires boosting.

PRIMARY AMEBIC MENINGOENCEPHALITIS (NAEGLERIA)

> CASE
>
> A 7-year-old boy presents with a history of a 6-day illness of fever, blocked nose, severe headache, nausea and vomiting. In hospital, he develops ***stiff neck*** and becomes progressively lethargic. ***CSF*** shows ***free-living structures*** which had irregular shape and changed constantly. It has non-directional motility with ***pseudopodia***.

- Naegleria (*Naegleria fowleri*) is a small, free living ameba.
- It causes human amebic meningoencephalitis.
- Naegleriais an ameboflagellate that can exist as cysts, trophozoites, and transient flagellate forms.
- Trophozoites are the only stages that are invasive.
- But under proper environmental conditions, cysts convert into vegetative forms and become potentially infective.
- Naegleria can be isolated from a variety of freshwater sources, including ponds and lakes, domestic water supplies and groundwater.
- Naegleriameningoencephalitis is reported during the summer months in previously healthy individuals who have a history of swimming in or contact with freshwater before illness.

Pathogenesis

- The free-living amebas enter the nasal cavity by inhalation or aspiration of water contaminated with trophozoites or cysts.
- Naegleriagains access to the central nervous system through the olfactory epithelium. It migrates via the olfactory nerve to the olfactory bulbs. Subarachnoid space is infected and then it spreads to other areas of the central nervous system.
- Infection causes widespread cerebral edema and hyperemia of the meninges. Olfactory bulbs are necrotic, hemorrhagic, and surrounded by a purulent exudate.
- Microscopically, the gray matter is severely affected.

Clinical findings

- The incubation of Naegleriainfection may be from 2-15 days.
- Symptoms are acute and progress rapidly.
- There is sudden onset of severe headache, fever, pharyngitis, nasal congestion or discharge, and nausea and vomiting, altered mental status, confusion, somnolence, seizures, and coma.
- Death may occur within 3–10 days after onset of symptoms.

Granulomatous amebic meningoencephalitis

- After weeks to months of initial infection, granulomatous amebic meningoencephalitis may develop.
- This presents as a single or multiple central nervous system space-occupying lesions.
- Clinical findings include hemiparesis, ataxia, personality (mental status) changes, seizures, and drowsiness.
- There is stiff neck and cranial nerve palsies, especially of cranial nerves III and VI.
- Granulomatous amebic meningoencephalitis is usually fatal after 4–6 weeks of illness.
- MRI or CT scan demonstrate multiple low-density lesions resembling infarcts or enhancing lesions of granulomas.

Diagnosis

- The CSF in *Naegleria* infection shows neutrophilic pleocytosis, elevated protein level, and hypoglycorrhachia.
- Using Wright or Giemsa stains, motile amebas may be visualized on a wet mount of freshly drawn CSF. Naegleria can also be grown on a non-nutrient agar plate.
- Diagnosis of granulomatous amebic meningoencephalitis depends on the isolation or histologic identification trophozoites or cysts from brain tissue specimens.

Management

- Naegleria infection is nearly always fatal.
- Early recognition and early management are important for complete cure.
- Main treatment of Naegleriainfection is amphotericin B, either alone or in combination with rifampin, chloramphenicol, fluconazole, or ketoconazole. Dexamethasone is also used.
- Duration of treatment should be at least 10 days.

WORM INFESTATION (HELMINTHIASIS)

- Helminths (worms) are parasites, with man as a host.
- The most common worm infestations are:
    - *Ascaris lumbricoides* (Round worm).
    - *Ancylostoma duodenale* (Hook worm).
    - *Enterobius vermicularis* (Pin worm).

ASCARIS LUMBRICOIDES: (ROUND WORM)

CASE

A 4-year-old boy from a poor family presents with cough and ***abdominal pain.*** There is history of pica. Full blood count shows ***eosinophilia***. There is history of passing many worms in stool.

- Ascariasis or round worm infestation is caused by *Ascaris lumbricoides.*
- Ascariasis is a very common infection, especially in preschool and younger children.
- Eggs of Ascaris *lumbricoides* are found in the soil, and humans are infected by contact with the soil. The eggs are ingested and hatch in the intestine, where they become larvae. The larvae penetrate the intestine, enter the venules or lymphatics, and subsequently reach the lungs, where they mature. Mature round worms then migrate up the bronchioles into the pharynx, where they are swallowed and finally pass into the small intestine, and the cycle is repeated.

Clinical findings

- Peak incidence is between 1–6 years of age.
- Most patients are asymptomatic.
- Abdominal pain, distension, or intestinal obstruction may occur with heavy infection.
- Pulmonary symptoms are rare and result from large numbers of larvae passing through the lungs, causing cough, blood stained sputum, eosinophilia, and pulmonary infiltrates (Loffler's syndrome).

Investigations

- Blood counts may show eosinophilia.
- Long, pink, and round worms may be passed in the stool or vomitus.
- Eggs are found in the stool and can be identified microscopically.

Management

- Mebendazole (100 mg twice daily for 3 days). Or
- Pyrantel pamoate (10 mg/kg as a single dose). Or
- Albendazole (200–400 mg as a single dose). Or
- Piperazine.

Prevention

- Proper hand washing.
- Adequate sanitary treatment and disposal of infected human feces.

ANCYLOSTOMA DUODENALE: (HOOK WORM)

- Larvae of *Ancylostoma duodenale* are found in warm, damp soil and infect humans by penetrating the skin.
- They migrate to the lungs, ascend the trachea, are swallowed, and reside in the small intestine.
- The worms then mature and attach to the intestinal wall, where they suck blood and shed eggs.

Clinical findings

- Infections usually are asymptomatic.
- Intense pruritus (ground itch) may be present at the site of larval penetration usually the soles of feet.
- There may be abdominal pain, anorexia, indigestion, fullness, and diarrhea.
- Major presentation of infection is anemia because *Ancylostoma duodenale* consumes 0.2–0.5 ml blood/worm/day.
- Chronic infection causes hypoalbuminemia, and edema, which may lead to heart failure.

Investigations

- In peripheral blood film, there is microcytic, hypochromic anemia and eosinophilia.
- Hookworm eggs are seen on examination of fresh stool specimen.

Management

- Pyrantel pamoate (10 mg/kg single dose). Or
- Mebendazole (100 mg twice daily for 3 days).
- Iron therapy for anemia.

Prevention

- Sanitation of the patient's environment. Fecal contamination of soil should be prevented.
- Skin contact with potentially contaminated soil should also be avoided.

ENTEROBIUS VERMICULARIS: (PIN WORM)

CASE

A 3-year-old boy presents with complaint of awaking at night with screaming, ***perianal irritation*** and itching. There is history of pica. His appetite has decreased and he occasionally complains of abdominal pain. Examination is normal. Inspection of the perianal region demonstrates superficial excoriations and several thread-like worms.

- Enterobiasis or pin worm infestation is a common infection in children caused by *Enterobius vermicularis*.
- The eggs of *Enterobius vermicularis* are passed on hands, clothing, and house dust.
- After ingestion, eggs hatch in the stomach, and the larvae migrate to the cecum and mature.
- Gravid females migrate at night to the perianal region to deposit their eggs, which are viable for 2 days.
- Scratching contaminates the fingers and allows transmission back to the host (auto-infection) or to the contacts.

Clinical findings

- The main symptom is nocturnal perianal pruritis causing sleeplessness.

Diagnosis

- Eggs can be detected by pressing adhesive cellophane tape against the perianal region in the morning.
- Adult worms may be seen by direct inspection of perianal region or stool sample.

Management

- Mebendazole (100 mg in a single oral dose), pyrantel pamoate, or albendazole. Repeat therapy after 2 weeks may be necessary because of re-infection.
- Therapy for all family members at the same time is also necessary to prevent re-infection.

Prevention

- Proper hand washing and personal cleanliness
- Fingernails should be trimmed and kept clean
- Scratching of perianal area should be avoided

Notes

CHAPTER 11

Respiratory Disorders

CHOANAL ATRESIA

CASE

A full-term newborn infant presents with ***episodes of cyanosis and apnea***, which are ***worse when he is attempting to feed***. He ***seems better when he is crying***. A ***feeding tube is not passed*** down either nares.

- Choanal atresia consists of a unilateral or bilateral septum between the nose and the pharynx:
  - Bony septum in 90% cases
  - Membranous septum in 10% cases
- Frequency is approximately 1 in 7,000 live births.
- Most cases are a combination of bony and membranous atresia.
- The unilateral defect is more common.
- Female: male ratio is approximately 2: 1.

Associations

- CHARGE syndrome
- Treacher-Collins syndrome
- Kallmann syndrome
- VATER (vertebral defects, imperforate anus, tracheoesophageal fistula, and renal defects) association
- CHARGE syndrome (**c**oloboma, **h**eart disease, **a**tresia choanae, **r**etarded growth and development or central nervous system anomalies or both, **g**enital anomalies or hypogonadism or both, and **e**ar anomalies or deafness or both)

Pathogenesis

- Persistence of the buccopharyngeal membranes or
- Failure of the oronasal membrane to rupture

Clinical findings

- When the obstruction is unilateral, the infant may be asymptomatic. Unilateral nasal discharge or persistent unilateral nasal obstruction can suggest the diagnosis.
- Infants with bilateral choanal atresia have vigorous attempts to inspire and develop cyanosis. Cry relieves the cyanosis. Cycle of cyanosis is repeated after closing their mouths.

Diagnosis

- There is inability to pass a firm catheter through each nostril 3-4 cm into the nasopharynx.
- Atretic plate can be seen directly with fiberopticrhinoscopy.
- The anatomy is best evaluated by CT scan.

Management

- Immediate treatment consists of:
  - Prompt placement of an oral airway
  - Maintaining the mouth in an open position
  - Intubation if needed (usually intubation or less often tracheotomy is indicated in bilateral choanal atresia)
- If there is no other serious medical problem, operative intervention is indicted in the neonatal age.
- Transnasal repair is the treatment of choice.
- Tracheotomy should be considered in cases of bilateral atresia when there are other life-threatening problems are present and surgical repair is not possible.
- If there are other problems in a case of unilateral choanal atresia, operative correction of unilateral obstruction may be deferred for several years.
- In both unilateral and bilateral cases, restenosis may occur and dilation or reoperation, or both may be needed.
- Mitomycin C is effective to prevent the development of granulation tissue and stenosis.

ACUTE RESPIRATORY INFECTIONS (ARI)

Acute Respiratory Infections (ARI) is the leading cause of illness and death of children under 5 years of age. ARI constitutes 30–60% of patients in a hospital outpatient. Eighty percent of these children have acute upper respiratory infections (AURI). Most of these AURI are self-limiting and only require symptomatic treatment except for middle ear infections or streptococcal sore throat.

Nearly 20% of ARI patients develop acute lower respiratory infections (ALRI). Majority of these are pneumonia. Approximately 250,000 children <5 years of age die due to pneumonia in Pakistan every year.

- National ARI control Programme was launched with the following two objectives:
  - Reduce mortality of children less than 5 years of age due to pneumonia
  - Rationalize the use of antibiotics and other drugs in ARI
- The following strategies were adapted:
  - Standard case management of ARI patients based on WHO guidelines
  - Immunization
  - Improved feeding practices especially breastfeeding

Etiology

Bacterial pneumonia is more common in Pakistan. In contrast pneumonia in developed countries is mostly viral. The most common bacteria isolated from cases of acute lower respiratory infections in children were:

- *Streptococcus pneumonia.*
- *Haemophilusinfluenzae.*

- *Staphylococcus aureus.*
- *Group A. Streptococci.*

Simple clinical signs

The WHO (World Health Organization) studies have shown the following two signs to be the most critical and sensitive for diagnosis of pneumonia.

1. Fast breathing.
2. Lower chest indrawing.

Therefore, the cut-offs for respiratory rate/minute for the diagnosis of pneumonia are:

Table 11.1: Clinical signs for pneumonia.

If the child is:	Then he has fast breathing if you count:
Less than 2 months	60 breaths/minute or more
2 months up to 11 months	50 breaths/minute or more
12 months up to 5 years	40 breaths/minute or more

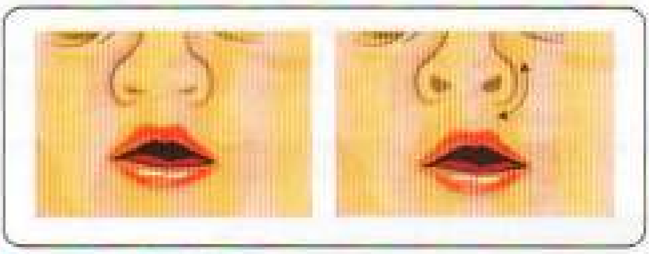


Figure 11.1: Nasal flaring.

Rational use of drugs in ARI

- More than 80% of ARI cases have cough or cold or AURI. These patients do not need antibiotics. Use of variety of cough syrups, with potentially harmful ingredients, is unnecessary and may be dangerous. These patients may be given simple non-sedative cough mixture or a home remedy.
- Recommended home remedies are:
    - Green tea with honey
    - Qahwa
    - Joshanda

ACUTE PHARYNGITIS

CASE

Acute pharyngitis and tonsillitis: A 4-year-old child presents with (***high-grade fever***) temperature of 101.3°C (38.5°C) and a ***sore throat***. On examination, there is exudative pharyngitis and bilateral, anterior ***cervical lymphadenopathy***.

- Pharyngitis is defined asinflammation of the pharynx, including any of the following:
    - Erythema
    - Edema
    - Exudates
    - Enanthem (ulcers, vesicles)

Infectious Etiologies

Viruses

- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus
- Adenoviruses
- Rhinoviruses
- Epstein-Barr virus
- Herpes simplex virus

Bacteria

- Group A streptococcus
- Mycoplasma pneumonia
- Chlamydia trachomatis
- Corynebacterium diphtheria
- Haemophilusinfluenzae
- Streptococcus pneumonia

Clinical findings

- Most viral pharyngitis, except infectious mononucleosis, is mild. Common nonspecific symptoms such as rhinorrhea and cough develop gradually before they become prominent.
- Gingivo-stomatitis and ulcerating vesiclesthroughout the anterior pharynx and on the lips are seen in oral herpes simplex virus infection. High fever and difficulty taking oral fluids are common.
- Intense, diffuse pharyngeal erythema and Koplik spots (the pathognomonic enanthem) occur in measles.
- Splenomegaly or hepatomegaly may be the clue to Epstein-Barr virus infectious mononucleosis.
- Patients with group A streptococcus pharyngitis present with fever, sore throat, exudative pharyngitis, and/or peritonsillar abscess. There may be neck pain and patient appears toxic. Enlarged and tender anterior cervical lymph nodes are frequently present. Headache, abdominal pain, and vomiting are frequently associated with the infection. Streptococcal pharyngitis is relatively uncommon before 2–3 years of age. It is common among children 5-15-year-old.
- Key physical findings in diphtheria are bull neck (extreme neck swelling) and a gray pharyngeal pseudomembrane that can cause respiratory obstruction.
- *M. pneumonia* cause pharyngitis, but other upper and lower respiratory infection findings are more common. Development of a severe or persistent cough subsequent to pharyngitis may be the clue to infection with this organism.

Diagnosis

- Streptococcal antibody tests are not useful in assessing patients with acute pharyngitis.

- **Throat culture** (gold standard) and **rapid antigen-detection tests** (RADTs) are the diagnostic tests for group A streptococcal infection.
- All RADTs have very high specificity, generally ≥95%, so when a RADT is positive, it is accurate and throat culture is unnecessary.
- Polymerase chain reaction testing for respiratory pathogens can identify a variety of viral and bacterial agents within a few hours.
- A complete blood cell count showing many atypical lymphocytes and a positive mononucleosis slide agglutination test can help to confirm a clinical diagnosis of infectious mononucleosis.

Management

- Specific therapy is not available for most viral pharyngitis.
- Symptomatic therapy is important.
- An oral antipyretic/analgesic agent (acetaminophen or ibuprofen) can relieve fever and sore throat pain.
- Systemic corticosteroids are sometimes used in upper airway compromise due to infectious mononucleosis but not in other types of pharyngitis.
- Antibiotic therapy of bacterial pharyngitis depends on the type of organism.
- Group A streptococcal pharyngitis may resolve uneventfully within 5 days.
    - Early antibiotic therapy hastens clinical recovery and can prevent Acute Rheumatic Fever (ARF) if started within 9 days of onset of illness.
    - Antibiotic therapy does not prevent Acute Poststreptococcal Glomerulonephritis (APSGN).
    - Group A streptococci are susceptible to penicillin and all other β-lactam antibiotics. The duration of oral penicillin and amoxicillin therapy is 10 days. A single intramuscular dose of benzathine penicillin is effective.
    - Patients allergic to penicillin can be treated with a 10 days course of cephalexin, cefadroxil, erythromycin, clarithromycin, or clindamycin, or for 5 days with azithromycin.

Complications

- Middle ear infections
- Bacterial sinusitis
- Complications of GAS pharyngitis:
    - Local suppurative complications, such as parapharyngeal abscess.
    - Non-suppurative illnesses, such as Acute Rheumatic Fever (ARF), Acute Poststreptococcal Glomerulonephritis (APSGN), Poststreptococcal Reactive Arthritis, and possibly PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with *S.pyogenes*) or CANS (Childhood acute Neuropsychiatric Symptoms).

Prevention

- Antimicrobial prophylaxis with daily oral penicillin prevents recurrent group A streptococcal infections. It is recommended only to prevent recurrences of ARF.

TONSILS AND ADENOIDS

CASE

A 7-year-old child has presented with ***recurrent rhinorrhea***. He is a ***persistent mouth breather***. He has history of otitis media. On examination, temperature is normal, chest is clear, respiratory rate is 28/minute.

- Tonsils and adenoid provide primary defense against many microorganisms.
- Most episodes of acute pharyngo-tonsillitis are caused by viruses. Group Aβ-Hemolytic Streptococcus (GABHS) is the most common cause of bacterial infection in the pharynx.
- Tonsils and adenoids can be chronically infected by multiple microbes, which can include streptococci and *H. influenzae*.
- Both the tonsils and adenoids are a major cause of upper airway obstruction in children.

Clinical findings

- Symptoms of Group A Beta-Hemolytic Streptococcal (GABHS) infection include odynophagia, dry throat, malaise, fever and chills, dysphagia, referred otalgia, headache, muscular aches, and enlarged cervical nodes. Signs include dry tongue, erythematous enlarged tonsils, tonsillar or pharyngeal exudate, palatine petechiae, and enlargement and tenderness of the jugulodigastric lymph nodes.
- Chronic tonsillitis present with halitosis, chronic sore throats, foreign-body sensation, or a history of expelling foul-tasting secretions. Examination reveals tonsils with debris within the crypts.

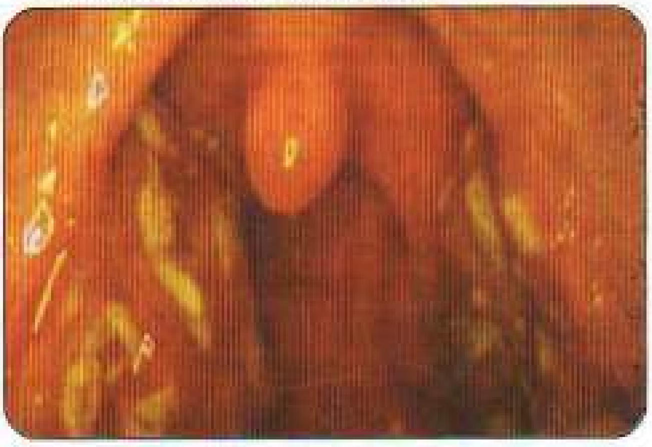


Figure 11.2: Follicular tonsillitis in a child.

- Symptoms of airway obstruction, secondary to adenotonsillar hypertrophy, include:

  - Chronic mouth breathing, nasal obstruction, hyponasal speech, hyposmia, decreased appetite, poor school performance, and symptoms of right-sided heart failure.
  - Night time loud snoring, choking, gasping, frank apnea, restless sleep, diaphoresis, enuresis, and sleep talking.
- Large tonsils are typically seen on examination.
- Size of the adenoid tissue can be demonstrated on a lateral neck radiograph or with flexible endoscopy.

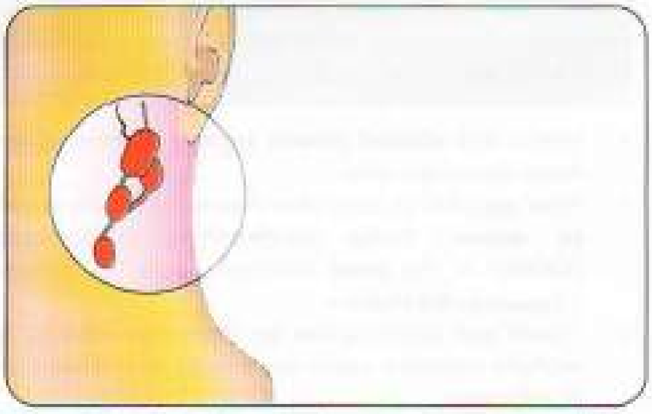


Figure 11.3: Cervical lymphadenopathy in acute tonsillitis.

Management

Medical management

- Treatment is same as the treatment of acute pharyngotonsillitis and GABHS.

Tonsillectomy

- Tonsillectomy is performed for recurrent or chronic pharyngotonsillitis.
- Tonsillectomy reduces the number of infections and the symptoms of chronic tonsillitis (halitosis, persistent or recurrent sore throats, and recurrent cervical adenitis).
- Resistant cases of cryptic tonsillitis are cured by tonsillectomy.

Adenoidectomy

- Adenoidectomy may be indicated for:
  - Chronic nasal infection (chronic adenoiditis)
  - Chronic sinus infections that have failed medical management
  - Recurrent bouts of acute otitis media
- Adenoidectomy may be curative in the management of nasal obstruction, chronic mouth breathing, and loud snoring suggesting sleep-disordered breathing.

Complications

- Poststreptococcal glomerulonephritis
- Acute rheumatic fever
- Peritonsillar infection (cellulitis or a frank abscess in the region superior and lateral to the tonsillar capsule)
- Retropharyngeal space infection
- Parapharyngeal space infection
- Chronic airway obstruction

ACUTE EPIGLOTTITIS

CASE

A 6-year-old boy presents in emergency room with a 3 hours (acute) history of ***high-grade*** fever to 39.5°C (103.1°F), and ***sore throat***. Child appears alert but anxious and toxic. There is mild ***inspiratory stridor*** and he is ***drooling***. There is a ***characteristicsitting posture*** with the ***neck hyperextended***.

- Epiglottitis refers to infection of the epiglottis, the aryepiglottic folds and arytenoid soft tissues.

Epidemiology

- The condition occurs mostly in the winter months, affecting males more often. It rarely occurs before 2 years of age, and the peak incidence is between 2–5 years.
- It is a bacterial infection, the commonest organism being *H. influenzae type b*.
- The incidence of acute epiglottitis may be markedly decreased due to the use of the *H. influenzae type b* vaccine. Therefore, other agents, such as *Streptococcus pyogenes*, *Streptococcus pneumonia*, nontypeable*H. influenzae*, and *Staphylococcus aureus*, represent a larger portion of epiglottitis in vaccinated children.

Pathogenesis

- Infection arises from direct invasion by the organism, with subsequent bacteremia.
- There is marked edema and evidence of inflammation with polymorphs and fibrin deposition.

Clinical findings

- Preceding upper respiratory tract infection
- Abrupt onset of high-grade fever (39–40°C)
- Moderate-to-severe respiratory distress
- Stridor
- Drooling because of the inability to swallow normally
- Irritability and restlessness
- There is often a choking sensation and the child sits, leaning forward.
- Complete obstruction of the airway is seen and death can ensue unless adequate treatment is provided.
- The barking cough typical of croup is rare. Usually, no other family members are ill with acute respiratory symptoms.
- **Note:** Physical examination should be done quickly and with care to minimize anxiety. Even a slight increase in restlessness may cause complete obstruction of the airway by the swollen epiglottis.
- A large, cherry red, swollen epiglottis is visualized by laryngoscopy under controlled circumstances (an operating room or intensive care unit).

Diagnosis

- Leucocytosis is very common, with counts more than 10,000/mm^3 and a predominance of polymorphs and immature neutrophils.
- Direct visualization (with a laryngoscope) of an enlarged, swollen, erythematous epiglottis is diagnostic.
- A lateral film of the soft tissues of the neck reveals evidence of epiglottitis. The presence of the 'thumb-printing sign' is a common radiographic marker for epiglottitis.

Differential diagnosis

- Viral croup (acute laryngotracheitis)

Management

- This is generally an emergency
- Secure the airway (with an artificial airway placed under controlled conditions)
- Oxygen is given by mask
- Best treatment is nasotracheal intubation. The patient should be given ventilatory support until edema subsides (usually after several days).
- Get bacterial swabs for culture at the time of intubation.
- Fluid and electrolyte support.
- Intravenous antibiotic therapy is given for 7–10 days. Initial agents of choice are:
    - Ceftriaxone 100 mg/kg/day
    - Cefotaxime
    - Meropenem
    - Chloramphenicol 50–75 mg/kg/day
- Indications for rifampin prophylaxis(20 mg/kg orally once a day for 4 days; maximum dose: 600 mg) is indicated for all household members. Household contacts include a:
    - Child within the home who is younger than 4 yrs of age and incompletely immunized
    - Child younger than 12 months of age and has not completed the primary vaccination
    - Immunocompromised person
- Acute laryngeal swelling due to an allergic reaction is best treated with:
    - Epinephrine (1: 1,000 dilution in dosage of 0.01 ml/kg to a maximum of 0.5 ml/dose) administered intramuscularly
    - Racemic epinephrine (dose of 0.5 ml of 2.25% racemic epinephrine in 3 ml of normal saline)
    - Corticosteroids are often needed (1–2 mg/kg/24 hours of prednisone for 3–5 days)

Prognosis

- After insertion of the artificial airway, patient improves immediately, and respiratory distress and cyanosis disappear.
- Epiglottitis resolves after a few days of antibiotics, and the patient may be extubated but antibiotics are given for 10 days.

CROUP (ACUTE LARYNGOTRACHEITIS)

CASE

2-year-old boy presents with ***noisy breathing on inspiration***, marked retractions of the chest wall, flaring of the nostrils and a ***barking cough*** and hoarseness. Cough is worsening at night. He has a mild upper respiratory infection (URI) for 3 days. Father has a cold the previous week. On examination, he has an axillary temperature of 100.4°F (38°C), respiratory rate 55 breaths/minute and heart rate 140 beats/minute.

- Croup is a term used for a respiratory distress with inspiratory stridor, cough (barklike or brassy) and hoarseness resulting from obstruction in the region of the larynx, trachea or bronchi.

Epidemiology

- Most patients with croup are between the ages of 3 months and 5 years, with the peak in the 2nd year of life.
- It is more common in boys and in the winter months.
- Spread of the causative virus is person to person. Approximately 15% of patients have a strong family history of croup.

Etiology

- Para-influenza viruses (type 1, 2 and 3) account for approximately 75% of cases
- Influenza A and B viruses
- Adenovirus
- Respiratory syncytial virus
- Measles virus

Pathophysiology

- Initial infection occurs in the nasopharynx.
- It then extends to the larynx and trachea, causing redness and swelling and ultimately narrowing of the lumen by the fibrinous exudate.

Clinical findings

- Viral croup usually has a gradual onset and course.
- Symptoms are often worse at night.
- Initially, the child gets a cold, with cough, coryza and low-grade fever.
- Gradually (in 12–48 hours) cough becomes 'croupy' i.e. barky with inspiratory stridor, causing varying degrees of respiratory distress with retractions and even cyanosis.
- Examination reveals hoarse voice, coryza, a normal or minimally inflamed larynx and an increased respiratory rate with prolonged inspiratory phase and stridor.
- The duration of symptoms is usually 3–7 days.
- Other family members might have mild respiratory illnesses with laryngitis.

Diagnosis

- Diagnosis is usually apparent from the clinical features.
- Croup is a disease of the upper airway, and alveolar gas exchange is usually normal. Hypoxia and low oxygen saturation usually is not present unless there is complete airway obstruction. If the child is hypoxic, cyanotic, pale or obtunded, immediate airway management is needed.
- X-ray of soft tissues of neck (lateral view) reveals subglottic narrowing (steeple sign).
- The white cell count is normal.

Complications

- Secondary bacterial infection
- Hypoxia with respiratory fatigue

Differential diagnosis

- Bacterial tracheitis
- Sudden onset of respiratory obstruction can be caused by aspiration of a foreign body
- Retropharyngeal or peritonsillar abscess
- Angioedema
- Hypocalcemictetany
- Croupy cough may be an early sign of asthma
- Epiglottitis

Management

- Main treatment includes:
    - Airway management
    - Treatment of hypoxia
- Treatment of the respiratory distress should be first priority before ordering any test.
- **Mist therapy:** It is given by hot steam from a vaporizer or cold steam from a nebulizer. Respiratory distress may improve within minutes but humidification should be continued until the cough subsides (usually after 2–3 days).
- Indications for hospitalization are: cyanosis, decreased level of consciousness, progressive stridor, or a toxic appearance.
- **Oxygen (cold and humidified)** should be provided.
- Patient should be disturbed as little as possible.
- Pulse oximetry and arterial blood gas analysis are important in assessing the adequacy of air exchange.
- **Nebulized racemic epinephrine** (a dose of 0.25–0.5 ml of 2.25% racemic epinephrine in 3 mL of normal saline can be used as often as every 20 minutes) if available may improve air exchange. Its effect is transient and repeated nebulization is needed.
- **Dexamethasone** (0.6 mg/kg administered once oral or I/M) is very effective to shorten the course of the illness.
- Use of **antibiotics** only if there is suspicion of secondary bacterial infection.
- **Contraindications:** Sedatives, expectorants, bronchodilators, and anti-histamines.

LARYNGOMALACIA

CASE

A 2-month-old infant presents with persistent noisy breathing (***inspiratory stridor***) since the first month of life. Otherwise he is well without any fevers. Physical examination is unremarkable except for moderate inspiratory stridor and retractions, which are ***worse*** when the infant is ***supine (sleeping)*** or ***agitated*** and ***better*** when he is ***prone*** and ***quiet***.

Clinical findings

- Laryngomalacia is the most common congenital laryngeal anomaly.
- It is the most common cause of stridor in infants and children.
- Stridor is inspiratory and low-pitched. It is exacerbated by any exertion (crying, agitation, or feeding).
- Stridor is caused by decreased laryngeal tone which leads to supraglottic collapse during inspiration.
- Clinical findings usually appear within the first two weeks of life and increase in severity for up to 6 months but may improve at any time.

Diagnosis

- Diagnosis is mainly clinical and is confirmed by flexible laryngoscopy.

Management

- Main treatment is observation because most infants resolve spontaneously as the infant and airway grow.
- If symptoms are severe enough to cause progressive respiratory distress, cyanosis, or failure to thrive, surgical intervention via supraglottoplasty is considered (90% successful in relieving upper airway obstruction caused by laryngomalacia).

OTITIS MEDIA

CASE

A 4-year-old child presents with 3 days history ***of fever*** and ***cold symptoms***. Now, he has developed ***right ear pain***. Physical examination is normal except ***bulging tympanic membrane***.

- Otitis media is one of the most common infections of childhood, especially between the ages of 6 months to 3 years.

Definition

- **Acute otitis media** is defined as inflammation of the middle ear presenting with rapid onset of symptoms.
- **Recurrent otitis media** is defined as three new acute otitis media episodes within 6 months or four episodes during 1 year.

- **Chronic otitis media** is defined as persistent discharge from the ear longer than 6 weeks.

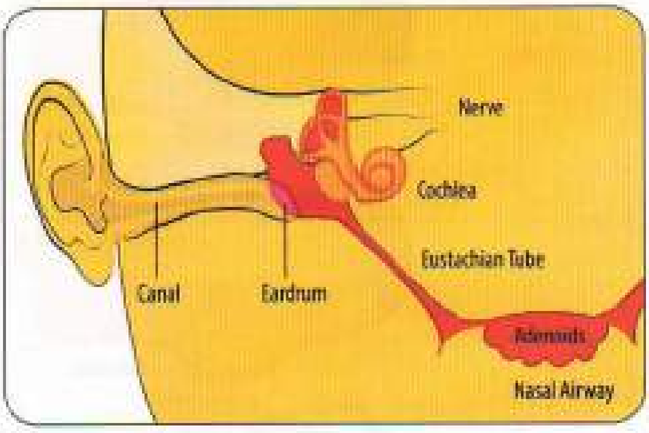


Figure 11.4: Anatomy of middle ear.

Etiology

- **Bacteria** are the most common agents causing otitis media. The most common organisms are:
  - Streptococcus pneumonia (25–40%)
  - Haemophilusinfluenzae (15–25%). It causes recurrent otitis media
  - Moraxella catarrhalis (12–20%)
  - Group A streptococcus
  - Staphylococcus aureus (acute and chronic otitis media)
  - Pseudomonas aeruginosa (chronic otitis media)
- **Viruses** are not important direct cause of otitis media. However, viral upper respiratory infections commonly result in obstruction of the eustachian tube, which allows bacteria to multiply in the middle ear space.

Pathogenesis

- Bacteria gain access to the middle ear when the normal patency of the eustachian tube is blocked by local infection, pharyngitis, or hypertrophied adenoids.
- Obstruction of the flow of secretions from the middle ear to the pharynx, result in a middle ear effusion that become infected by bacteria.

Predisposing factors

- The following factors are associated with an increased incidence of otitis media in childhood.
  - Age less than 1 year
  - Immunodeficiency
  - Down syndrome
  - Structural defects that impair eustachian tube function (e.g. cleft palate)
  - Siblings with recurrent otitis media
  - Passive smoking
  - Children with lower socio-economic status
- Breastfeeding reduces the incidence of acute respiratory infections and prevents colonization with otitis pathogens through selective IgA antibody.

Clinical findings

- Neonates and infants may be asymptomatic or may present with only non-specific manifestations such as irritability, fever, diarrhea, vomiting, or may pull at their ears.
- Non-specific signs and symptoms in children are fever, irritability, mild upper respiratory symptoms, vomiting and diarrhea.
- Classic signs and symptoms of acute otitis media are pain in one or both ears and hearing loss. A discharge from the ear may be present.
- Chronic otitis media presents with hearing impairment, perforation of the tympanic membrane, and a foul-smelling discharge from the ear canal (otorrhea).

Diagnosis

- Otoscopy and tympanometry:
  - Abnormal contour of tympanic membrane, which consists of fullness or bulging or extreme retraction.
  - Erythema of tympanic membrane is present. Presence of liquid in middle ear cavity may impart pale yellow color.
  - Opacification of tympanic membrane is present.
  - Structural changes of tympanic membrane include scars, or perforation.
  - Mobility of tympanic membrane is impaired. Mobility is the most sensitive and specific in determining presence or absence of middle ear effusion.
- Culture of the ear discharge.
- Needle aspiration and culture of the middle ear contents (in cases where there is no ear discharge) is the most reliable method for confirming the presence of infection and identifying the causative agent.

Complications

- Mastoiditis
- Meningitis
- Hearing loss

Management

Acute otitis media

- Dry mopping of the ear
- Analgesics for pain
- Antipyretics for fever
- Initial treatment is directed against the most common organisms (*S. pneumoniaand H. influenzae*). Antibiotics are changed according to the culture and sensitivity report. The drug of choice is amoxicillin (80–90 mg/kg/day in three divided doses for 10 days), which usually is effective against both of these organisms.
- Alternative antibiotics are amoxicillin-clavulanic acid, erythromycin-sulfisoxazole, cefaclor, cefuroxime, trimethoprim-sulfamethoxazole, and cefixime. The duration of therapy is 7–10 days.
- For penicillin-resistant pneumococci, options include ceftriaxone 50 mg/kg/day IM once a day for total 1–3

doses, or macrolide antibiotic (azithromycin, clarithromycin).

- Patients who are not cured after a second course of antibiotics or who become severely ill may be considered for tympanocentesis to identify the causative pathogen so that appropriate antibiotic can be used.

Recurrent otitis media

- Patients with recurrent otitis media may be placed on daily doses of an antibiotic such as sulfisoxazole or amoxycillin prophylaxis for 3–6 months after acute infection has cleared.

Chronic suppurative otitis media

- The pathogens are usually mixed and commonly include *S. aureus*, *P. aeuroginosa*, or both. Initial therapy with an oral antibiotic that is effective against *Staphylococcus* is tried, but optimal therapy is based on middle ear cultures and may require intravenous anti-pseudomonal therapy.

Chronic otitis media with effusion

- May be due to infection, allergy or immunologic disorders
- 2–4 weeks course of oral antibiotic may be effective
- In resistant cases, placement of tympanostomy tubes is recommended for more than 2–3 months

BRONCHIOLITIS

CASE

A 3-month-old infant presents with a history of ***cough*** and ***runny nose*** for 3 days. He has now developed ***difficulty breathing***. Two other members of the family have similar symptoms. On examination, he has marked ***intercostal and subcostal retractions*** with nasal flaring. On auscultation, there is ***diffuse wheezing*** all over the chest. He is mildly hypoxic. Chest radiograph displays a diffuse interstitial infiltrate with mild hyperinflation. A rapid RSV antigen test is positive.

Definition

- Bronchiolitis is an inflammatory disease of the bronchioles.

Incidence

- It is common disorder in infants and occurs in 6–7% of infants below 2 years of age (due to their small airways). Peak age of onset is 6 months.
- Boys predominate 2 to 1 is more common between December and March (winter, spring).
- Bronchiolitis is less common in breastfed.
- It is more common in those who live in crowded conditions.
- Older family members are a common source of infection in infants.

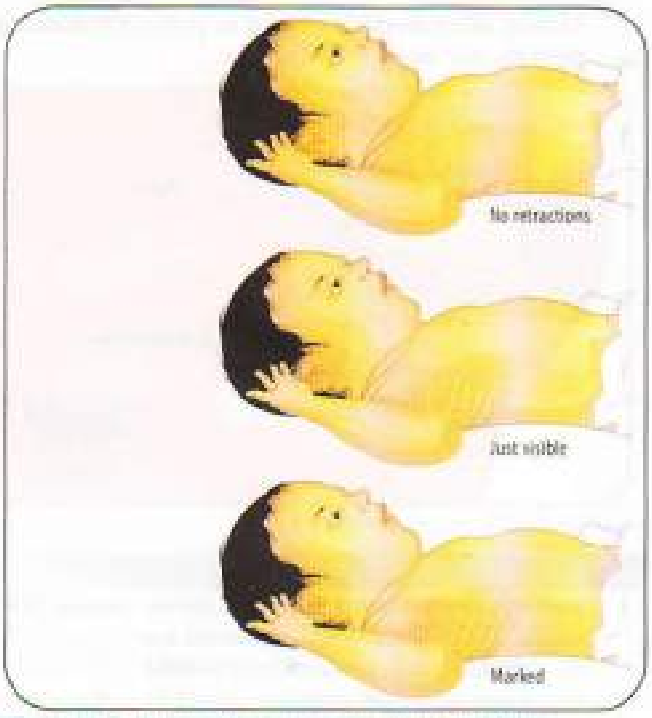


Figure 11.5: Lower chest retractions in bronchiolitis

Etiology

Acute bronchiolitis is predominantly a viral disease.

- Respiratory syncytial virus (RSV) is the most common causative agent (in more than 50% of cases).
- Para-influenza virus
- Adenovirus
- Rhinovirus
- Mycoplasma

Pathogenesis

- Viral invasion of bronchioles leads to inflammation and bronchiolar obstruction due to edema and accumulation of mucus and cellular debris.
- There is patchy involvement and some areas become emphysematous and other atelectatic.

Clinical findings

- The first clinical sign is an upper respiratory tract infection. Usually another family member is ill with respiratory infection. After 1–2 days of mild rhinitis, the infant develops increasing cough and breathe more rapidly. There is often feeding difficulty and vomiting and infant becomes irritable, though without much fever. Fever rarely goes beyond 39°C (102°F) and cyanosis may occur.
- Physical examination reveals an infant with rapid, shallow respiration (60–80/minute), flaring of alaenasi and use of accessory muscles of respiration, which result in subcostal and intercostal retractions, and there is expiratory wheezing or grunting. Liver and spleen may be palpable as a result of depression of diaphragm due to hyperinflation.
- Percussion note is hyperresonant. The breath sounds are diminished and expiratory phase of breathing is

prolonged. In most severe cases breath sounds are barely audible (bronchiolitis obliterans).

Diagnosis

- The diagnosis of acute bronchiolitis is clinical.
- Acute bronchiolitis is suspected in a previously healthy infant presenting first time with a wheezing episode especially during winter season and a community outbreak.
- X-ray Chest is not indicated in every case of bronchiolitis. It reveals:
  - Hyperinflation of the lungs with increased lucency and increased anteroposterior diameter.
  - There are increased bronchovascular markings and mild infiltrates.
  - There may be patchy atelectasis.
- **White Blood Cell (WBC) counts** and differential counts are usually normal.
- **Viral culture** from nasopharyngeal secretions.
- **Viral antibody titer.**

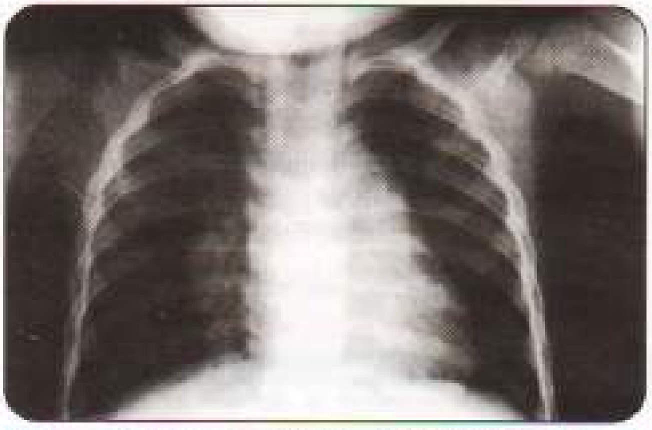


Figure 11.6: X-ray showing hyperinflation due to bronchiolitis.

Complications

- Pneumonia with superadded bacterial infection
- Pneumothorax
- Dehydration
- Respiratory acidosis
- Respiratory failure
- Heart failure
- Prolonged apneic spells and death may occur (less than 1%)

Differential diagnosis

Bronchial asthma

- Rare below 1 year of age.
- Family history of asthma.
- Repeated attacks in the same infant.
- Good response to adrenaline.

Bronchopneumonia

- Fever is high grade
- Child is more toxic
- Leukocytosis

Congestive heart failure

- Tachycardia
- Enlarging liver
- Other abnormal heart findings

Pertussis

- Bouts of cough
- No X-ray findings
- Lymphocytosis

Foreign body aspiration (sudden onset of illness

Cystic fibrosis

- Repeated respiratory infections
- History of malabsorption (steatorrhea)
- Increased sweat chloride concentration

Risk factors for severe disease

- Age <12 weeks
- Preterm birth
- Underlying comorbidity such as cardiovascular, pulmonary, neurologic, or immunologic disease

Management

- Infants with severe respiratory distress (hypoxia, inability to take oral feedings, apnea, and extreme tachypnea) should be hospitalized.
- Management is mostly symptomatic.
- Oxygen inhalation. Humidified cool oxygen is given to relieve hypoxia.
- Frequent suctioning of nasal and oral secretions is needed to relieve distress or cyanosis.
- Prop-up position with 30–40^0 angle.
- Intravenous or oral fluids to prevent dehydration.
- Correct respiratory acidosis and electrolyte imbalance.
- Ribavirin is an antiviral agent that can be used for treatment of severe bronchiolitis due to respiratory syncytial virus in infants who have congenital heart disease or chronic lung disease. Its use is controversial in otherwise healthy infants.
- Sedatives should be avoided. They can depress respiratory drive.
- Antibiotics are recommended in severe cases with superadded bacterial infection. Otherwise antibiotics are not indicated.
- Bronchodilators may provide short term improvement.
- Steroids are not effective.
- Heliox given by tight fitting mask or by continuous positive airway pressure may give some improvement in moderate to severe bronchiolitis.

Prognosis

- Infants with acute bronchiolitismay be at risk to develop respiratory compromise within 48–72 hours of illness.
- Case fatality rate is <1%
- Death may be due to:
  - Apnea
  - Respiratory arrest
  - Severe dehydration

- Duration of symptoms may persist up to 3 weeks (median duration 14 days).
- There is a higher incidence of wheezing and asthma in children with a family history of asthma or other atopic syndromes.

Prevention

- RSV intravenous immunoglobulin.
- Palivizumab, an intramuscular monoclonal antibody to the RSV F protein.
- Meticulous hand washing may help to prevent nosocomial transmission.

PNEUMONIA

CASE

A 2-year-old boy develops a ***cough***, coryza and ***fever*** of 104°F. Physical examination shows fever, mild ***tachypnea***, ***reduced air entry*** at the right base and crackles on auscultation. Chest radiograph shows consolidation of the right lower lobe. The white blood cell count is 22,000/μL with 78% polymorphonuclear leukocytes, 18% of which are band forms.

Definition

- It is defined as inflammation of the lung parenchyma, and is associated with consolidation of the alveolar spaces.
- Lung parenchyma is the portion of the lower respiratory tract consisting of the respiratory bronchioles, alveolar ducts, alveolar sacs, and alveoli.

Incidence

- It is a common problem in children and accounts for 10–20% of hospital admissions.
- It may be difficult to differentiate viral from bacterial pneumonia, especially as bacterial cultures are often negative.

Classification

Anatomic classification

- Bronchopneumonia (scattered inflammation of the lung around the bronchioles causing patchy involvement and consolidation of lung).
- Lobar pneumonia (consolidation of one or more lobes of the lung).
- Pneumonitis (patchy inflammation of the lung that may or may not be associated with consolidation).
- Interstitial pneumonitis (inflammation of the interstitial tissue, which is composed of the walls of the alveoli, alveolar sacs and ducts, and the bronchioles).

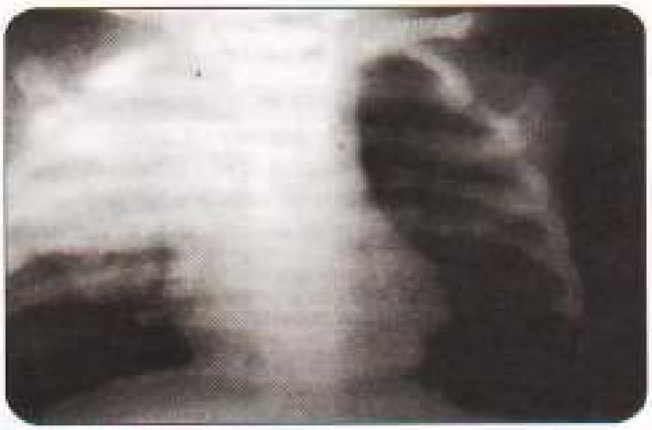


Figure 11.7: X-ray chest: Lobar pneumonia in right upper lobe.

Etiologic classification

- Bacterial pneumonia
- Viral pneumonia
- Aspiration pneumonia
- Hypostatic pneumonia
- Fungal pneumonia
- Protozoal pneumonia (due to Mycoplasma, Pneumocystis carinii)
- Loffler's pneumonia (transient pulmonary infiltrates with eosinophilia)
- Inflammatory pneumonia (SLE, sarcoidosis, histiocytosis)
- Pneumonia due to toxic substances (hydrocarbons, smoke, dusts)

Recurrent pneumonia

- Recurrent pneumonia is defined as two or more episodes in a single year or three or more episodes ever, with radiographic clearing between occurrences.
- An underlying disorder should be considered if a child experiences recurrent pneumonia.

Table 11.2: Causes of recurrent pneumonia.

Hereditary disorders:
• Cystic fibrosis • Sickle cell disease
Immunological disorders:
• Brutonagammaglobulinemia • Severe combined immunodeficiency syndrome • Chronic granulomatous disease • Hyperimmunoglobulin E syndromes • Leukocyte adhesion defect
Disorders of cilia:
• Immotile cilia syndrome • Kartagener syndrome

Anatomical disorders:

- Pulmonary sequestration
- Lobar emphysema
- Gastroesophageal reflux
- Foreign body
- Tracheoesophageal fistula (H type)
- Bronchiectasis
- Aspiration (oropharyngeal incoordination)

BACTERIAL PNEUMONIA

Etiology

Following are common organisms causing pneumonia at various ages:

Newborn

- Escherichia coli
- Group B streptococci
- Staphylococcus aureus
- Klebsiella
- Pseudomonas

Infancy and early childhood

- Pneumococcus
- Streptococcus (group A)
- Haemophilusinfluenzae type b
- Staphylococcus aureus
- Mycoplasma
- Escherichia coli
- Klebsiella

Older children

- Pneumococcus
- Haemophilusinfluenzae type b
- Streptococcus (group A)
- Staphylococcus
- Mycoplasma
- Mycobacterium tuberculosis

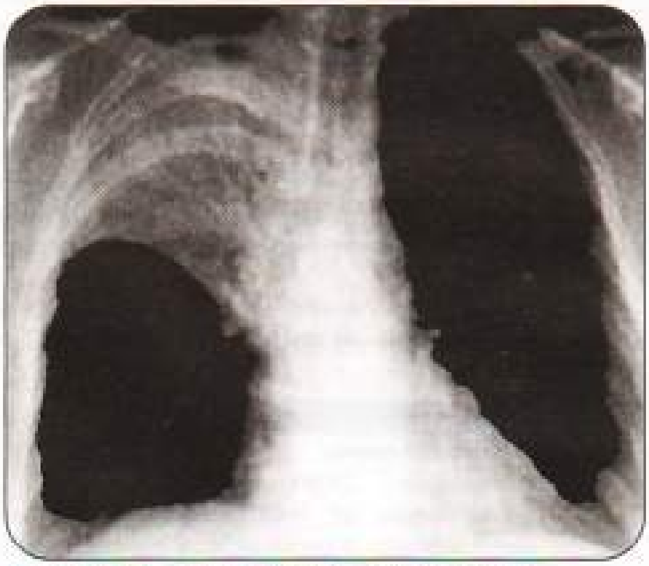


Figure 11.8: X-ray chest showing consolidation in pneumococcal pneumonia

Predisposing factors

- Repeated aspiration (esophageal reflux).
- Immunodeficiency or immunosuppression.
- Congenital anomalies (intrapulmonary sequestration, tracheo-esophageal fistula, cleft palate).
- Abnormalities in the clearance of mucus (cystic fibrosis, bronchiectasis, ciliary dyskinesia).
- Congestive heart failure (VSD, AV canal defects).

Pneumococcus

- The pneumococcus accounts for over 90% of childhood bacterial pneumonia.
- It classically causes a lobar pneumonia.
- Complications are relatively uncommon.

Streptococcus

- Streptococcus typically causes disease limited to the upper respiratory tract, but also may be responsible for lower respiratory tract disease.
- It causes empyema in about 25% of cases.
- It is more common after measles.

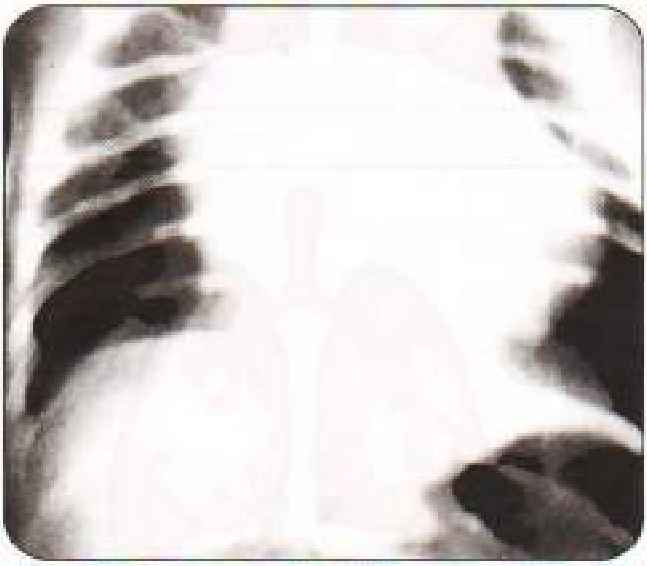


Figure 11.9: X-ray of a child having pneumonia in both lungs

Staphylococcus aureus

- Staphylococcus aureus is most commonly seen in the 1st year of life.
- Disease may be associated with a history of staphylococcal skin lesions.
- Clinical manifestations include an upper respiratory tract infection followed by the abrupt onset of high-grade fever, cough, and respiratory distress. The disease is rapidly progressive.
- There is bronchopneumonia early in the illness that rapidly progresses to lobar or complete involvement of a side of lung.
- Pleural effusion, empyema, or pneumatoceles are common complications.

Haemophilusinfluenzae Type b

- Pneumonia due to Haemophilusinfluenzae type b typically has an insidious presentation.
- Pneumonia usually is lobar, with extensive destruction of the small airways and interstitium.
- Pulmonary complications include pleural effusion and empyema.
- H. influenzae type b pneumonia is commonly associated with bacteremia, meningitis, cellulitis, or arthritis.

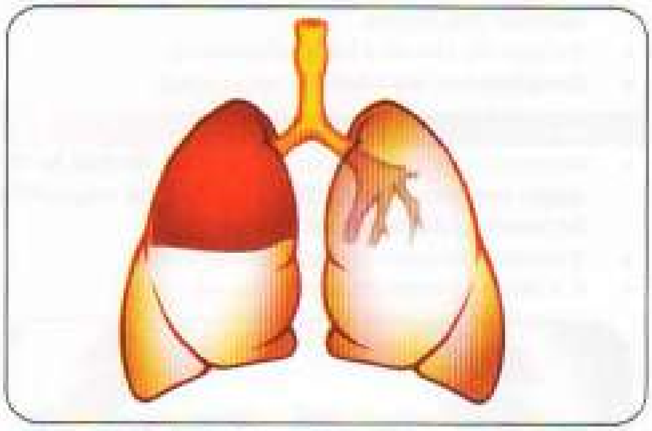


Figure 11.10: Illustration of lobar pneumonia.

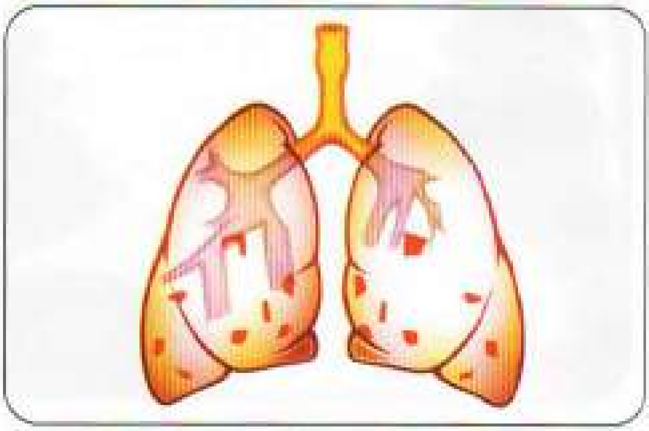


Figure 11.11: Illustration of bronchial pneumonia

Pathogenesis

- Respiratory tract below the vocal cords normally is sterile. Protective mechanisms are the mucus covering the mucosal epithelium, ciliary transport activity, cough reflex, and secretory IgA antibody present in mucosal secretions. Within the lung parenchyma, bacteria are cleared by lymphatics that drain to regional lymph nodes and by macrophages. Lungs are also protected by systemic humoral and cell-mediated immunity. Alteration of any of these protective mechanisms predisposes the child to develop bacterial pneumonia.
- Most bacterial pathogens are transmitted by close personal contact or air born spread. Pneumonia results from the aspiration of pathogenic bacteria into the lower respiratory tract. Sometimes it is preceded by viral infections (RSV, measles virus, influenza virus in 30–50% of cases), which disrupts the normal anatomic and physiologic barrier of the respiratory tract. Less frequently, bacteria spread to the lung hematogenously from a distant focus. In such cases, widespread pyogenic infection of other sites (meninges, bones, joints) may be present.

Clinical findings

- There is frequently a preceding upper respiratory tract infection.
- The infant then becomes acutely ill, develops shaking chills and high-grade fever. Feeds are taken reluctantly. The child becomes drowsy, restless, and tachypneic (respiratory ratio becomes 2:1 or 3:1 instead of 4:1 with heart rate). Respiratory rate is very significant when >60/minute in the newborn, >50/minute in 2 months to 1 year age, and >40/minute in 1 year to 5 years of age.
- There is dry, hacking, non-productive cough. Dyspnea is associated with flaring of alaenasi and expiratory grunting. There may be intercostal and subcostal recessions and cyanosis may occur.
- In infants, diarrhea, vomiting, meningismus (in right upper lobe pneumonia) and convulsions may occur.
- Older children usually complain of chest pain and sometimes abdominal pain (in right basal pneumonia). Abdominal pain is common in lower-lobe pneumonia. The liver may seem enlarged because of downward displacement of the diaphragm secondary to hyperinflation of the lungs or superimposed congestive heart failure.
- Classic physical findings of consolidation appear on 2nd or 3rd day of illness and are characterized by diminished movement of the chest on affected side, dullness on percussion, increased vocal fremitus, bronchial breathing, and increased vocal resonance. Pleural rub may be present. As resolution occurs, moist rales are heard and signs of consolidation disappear. Later, cough may become productive of blood tinged mucous material.
- The presence of consolidation can be confirmed radiologically but in many children, physical findings are remarkably slight in contrast to radiological consolidation. With treatment clinical signs disappear within 48 hours but radiological signs may persist up to 4 weeks.
- There may be associated problems like measles, otitis media, congenital heart disease, malnutrition, or septicemia.

Diagnosis

- **White blood cell count:**
    - Leukocytosis 15,000–40,000/mm^3 with a predominance of neutrophils (this is more commonly seen in pneumococcal pneumonia)
    - White blood cell counts less than 5,000/mm^3 often are associated with grave prognosis.

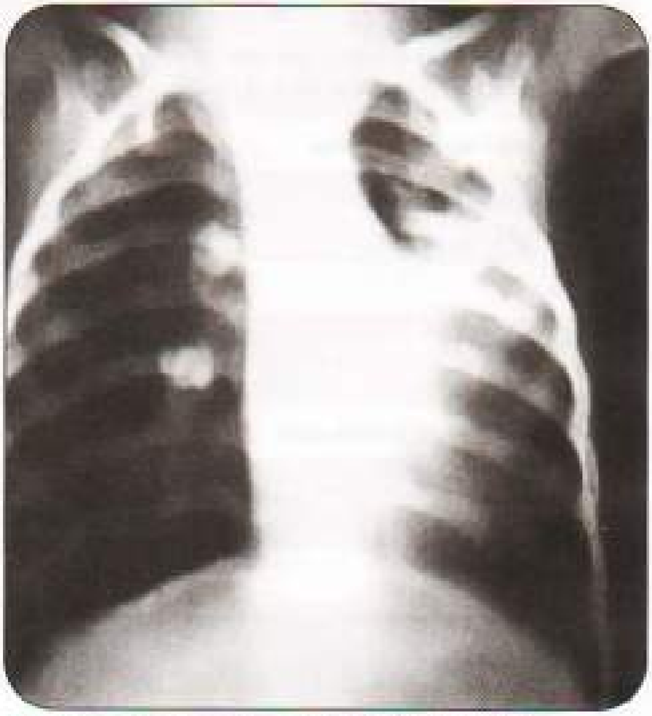


Figure 11.12: Chest X-ray: Left-sided pneumonia.

- **X-ray chest:**
    - It shows the extent and distribution of consolidation.
    - It also shows if there is pleural effusion or not.
    - In pneumococcal pneumonia, X-ray classically shows a lobar pneumonia with gross consolidation.
    - In streptococcal pneumonia, X-ray usually reveals a diffuse bronchopneumonia with large pleural effusions.
    - In staphylococcal pneumonia, X-ray may show a nonspecific bronchopneumonia early in the illness then rapidly progresses to lobar or complete hemi-thorax involvement.
    - In H. influenzae pneumonia, X-ray may show a lobar pneumonia, with extensive destruction of the small airways and interstitium.
- **Blood culture**
- **Gram staining** of expectorated sputum in older children
- **Pleural fluid examination** (if present)
- **ASO (anti-streptolysin O) titer** in case of streptococcal pneumonia
- **Tuberculin skin test**

Complications

- Empyema: It occurs frequently with *S. aureus, S. pneumonia*, and *S. pyogenes*.
- Lung abscess
- Pneumothorax
- Pneumatocele: These are thin-walled cavities that develop in the lung during the course of bacterial pneumonia. These are more common in staphylococcal pneumonia.
- Pleural effusion
- Delayed resolution
- Respiratory failure
- Metastatic septic lesions: Meningitis, otitis media, sinusitis, and septicemia may be present particularly with S. pneumonia or H. influenzae disease.

Management

Supportive management

- Bed rest and good diet
- Oxygen inhalation (2–4 L/minute)
- Antipyretics to lower the temperature. Expose the patient and give tepid water sponging if temperature is above 103°F
- Adequate fluid intake should be given because there is insensible water loss due to tachypnea
- Physiotherapy: Breathing exercise during recovery.

Specific management

- Specific antibiotics are given according to the causative agents for 7–10 days (2–3 weeks in case of staphylococcal pneumonia).
- When possible, therapy can be guided by the antibiotic sensitivity pattern of the organism isolated.

○ *Pneumococcus*	Benzyl Penicillin First generation cephalosporins
○ *Streptococcus:*	Benzyl Penicillin, Erythromycin
○ *Staphylococcus:*	First-generation cephalosporin, Cloxacillin
○ *H. influenzae:*	Second and third generation cephalosporins, Chloramphenicol
○ *Mycoplasma*	Erythromycin, Clarithromycin
○ *E. Coli:*	Aminoglycosides (Gentamicin, Amikacin)

- Tuberculosis: Anti-tuberculous drugs
- Pseudomonas/Klebsiella: For nosocomial pneumonia, commonly used regimens include meropenem (60 mg/kg/day divided in 3 doses), or piperacillin/tazobactam (240–300 mg/kg/day in 3–4 divided doses), or cefepine with or without gentamicin and vancomycin.

Treatment of complications

- Empyema: Drainage by aspiration or chest intubation
- Lung abscess: Postural drainage and physiotherapy

Prognosis

- If bacterial pneumonia is adequately recognized and treated, the survival rate is high.

Prevention

- Vaccination can reduce the incidence of pneumonia.
- Pneumococcal conjugate vaccine decreases pneumonia hospitalization rates.
- Influenza vaccine is also recommended.

PLEURAL EFFUSION

CASE

A 12-year-old boy presents with increasing shortness of breath. Physical examination reveals dullness at both bases. Chest X-ray reveals bilateral pleural effusions which are somewhat asymmetrical in size. Patient undergoes diagnostic thoracentesis. The fluid is straw colored.

Definition

- A pleural effusion is an excessive accumulation of fluid in the pleural space. It may be transudate or exudate.
- Pus in the pleural space is called empyema. Empyema is the most common cause of pleural effusion in children. It is due to *Streptococcus pneumonia*, *Haemophilusinfluenzae*, *Staphylococcus aureus*, and *Mycobacterium tuberculosis*.

Transudate

- Transudate occurs when there is imbalance between hydrostatic and oncotic pressure, so that fluid infiltration exceeds re-absorption.
- Transudate pleural effusions can be bilateral. Main causes include heart failure, hypoproteinemia (e.g. Nephrotic syndrome), and constrictive pericarditis.

Exudate

- Exudate occurs as a result of inflammation of the pleural surface leading to increased capillary permeability.
- Main causes of exudate include bacterial pneumonia, tuberculosis, connective tissue disorders, and malignancy.

Table 11.3: Differentiation of pleural effusion.

Appearance:	• Clear (T) • Cloudy or purulent (E)
Cell count (per mm^3)	• <1,000 (T) • Often >50,000 (E)
Cell type	• Lymphocytes, monocytes (T) • Polymorphonuclear leukocytes (neutrophils) (E)
Lactate dehydrogenase	• <200 U/L (T) • More than two-thirds upper limit of normal for serum Lactate Dehydrogenase (LDH) (E)
Pleural fluid : serum LDH ratio	• <0.6 (T) • >0.6 (E)
Protein >3 g	• Unusual (T) • Common (E)
Pleural fluid : serum protein ratio	• <0.5 (T) • >0.5 (E)
Glucose	• Normal (T) • Low (<40 mg/dL) (E)
pH	• Normal (7.40–7.60) (T) • <7.10 (E)
Gram stain	• Negative (T) • Occasionally positive (E)
Specific gravity	• Low <1.015 (T) • High (E)

T–Transudate

E–Exudate (Empyema)

Clinical findings

- There may be signs and symptoms of the underlying disease (e.g. pneumonia, heart failure, nephrotic syndrome). Pain, dyspnea and signs of respiratory insufficiency occur due to compression of the lung. In case of pneumonia and empyema, there is high-grade fever.
- Chest wall movements are reduced on affected side. Mediastinum is displaced towards the opposite side by the effusion. Percussion note will be stony dull. Breath sounds and vocal resonance are reduced or absent.

Diagnosis

- In a case of empyema, white blood cell **(WBC) count** is often elevated and blood cultures are sometimes positive.
- In a case of tuberculosis, **tuberculin skin test** may be positive.

- **X-ray chest:** The presence of pleural effusion is suggested by a homogenous opacity that obscures the underlying lung. Large effusions may cause a shift of the mediastinum to the contralateral side. Small effusions may only blunt the costophrenic angle.

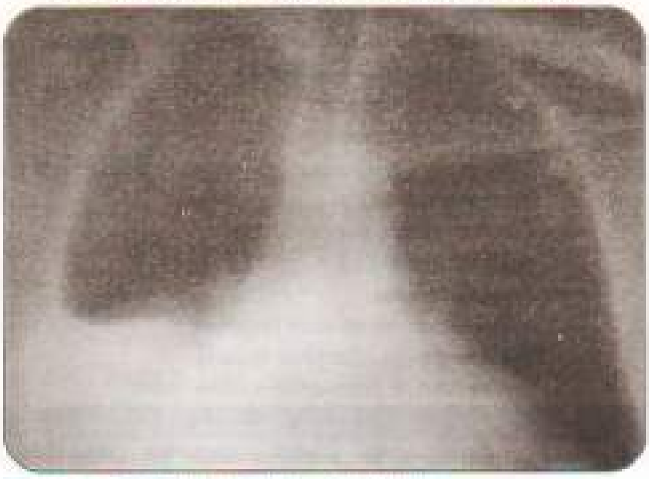


Figure 11.13: Right-sided pleural effusion.

- **Chest ultrasonography** can be valuable in localizing the fluid and detecting loculations.
- **Pleural fluid aspiration**, microscopic examination, and culture: Pleural fluid aspiration may reveal the effusion either exudate or transudate. Cells in the pleural fluid are usually neutrophils in bacterial disease and lymphocytes in tuberculous effusions. Gram stain, ZN stain, and cultures are often positive for the causative organism.
- **Pleural biopsy** may be necessary if the diagnosis is not established from the above aspiration.

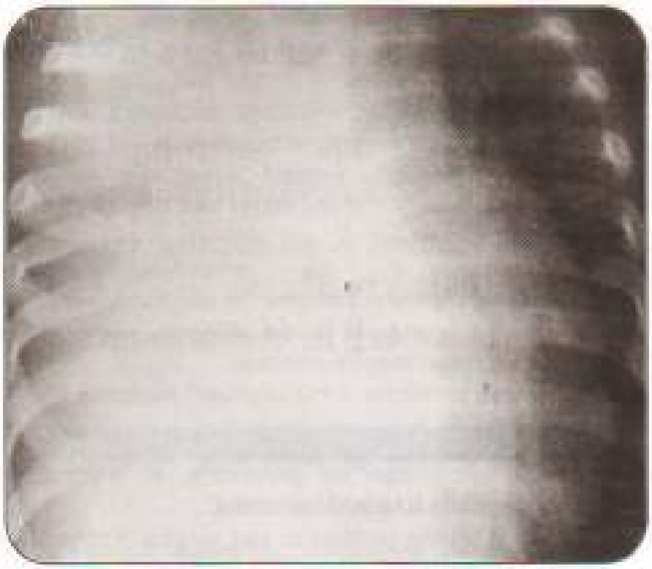


Figure 11.14: Right-sided massive pleural effusion.

Management

- Treatment is of the underlying condition that has caused the effusion (e.g. pneumonia, tuberculosis, nephrotic syndrome).

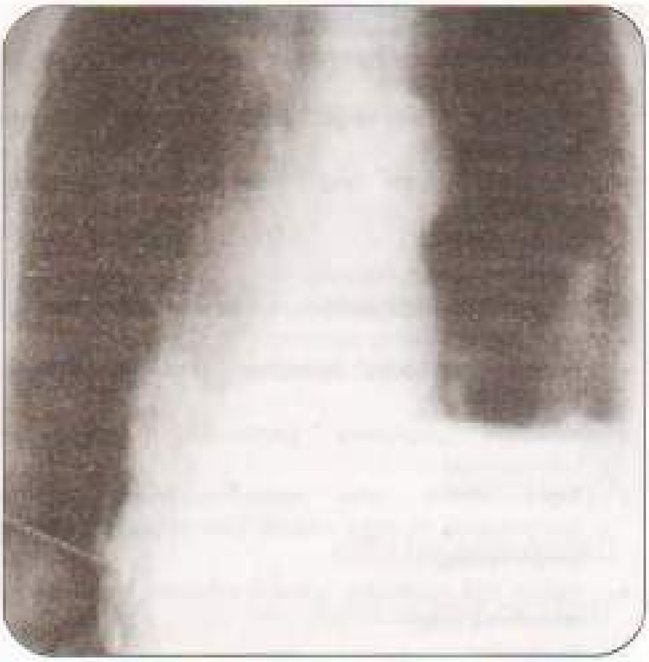


Figure 11.15: Pleural effusion left-sided.

- For small effusions (especially if they are transudative), usually no therapy is required, except the treatment of the cause.
- For large effusions, drainage with a chest tube, especially if the fluid is purulent (empyema), is needed.
- Appropriate intravenous antibiotics (for 2–4 weeks) should be given in a case of empyema or anti-tuberculous treatment in a case of tuberculous effusion.
    - For *staphylococcus* (Vancomycin, lincomycin, cephradine, cloxacillin)
    - For *Pneumococcus* (Benzyl penicillin, ceftriaxone, cefotaxime)
    - For *H. influenzae* (Cefotaxime, ceftriaxone, Ampicilin, chloramphenicol)

Prognosis

- The prognosis for patients with pleural effusions is excellent if the underlying condition is treated successfully.

BRONCHIECTASIS

CASE

A 10-year-old girl presents with ***chronic cough***, ***copious sputum production*** (green), and hemoptysis. There is history of ***recurrent chest infections***.

- Bronchiectasis is an irreversible abnormal dilation and anatomic distortion of the bronchial tree.
- It is common end stage of a many respiratory conditions (chronic suppurative .
- Females are affected more frequently than males.

Causes and associations

- Airway wall compression by vascular ring or adenopathy
- Recurrent pneumonia, pneumonia, or aspiration pneumonia
- Impaired cough (e.g. neuromuscular weakness conditions)
- Cystic fibrosis
- Primary ciliary dyskinesia
- Foreign-body aspiration causes airway obstruction
- Aspiration of gastric contents
- Immune deficiency syndromes (especially humoral immunity)
- Infection (especially pertussis, measles, and tuberculosis)
- Right middle lobe syndrome(chronic extrinsic compression of right middle lobe bronchus by hilar lymph nodes)
- Yellow nail syndrome (pleural effusion, lymphedema, discolored nails)
- Congenital:
    - Williams-Campbell syndrome (an absence of annular bronchial cartilage)
    - Marnier-Kuhn syndrome (congenital tracheobronchomegaly), in which there is a connective tissue disorder

Pathophysiology and pathogenesis

- Three basic mechanisms are involved in the pathogenesis of bronchiectasis.
    - Obstruction can occur due to impacted mucus, poor mucociliary clearance, external compression, bronchial webs, and atresia. Bronchial lumen ends abruptly because of mucous plugging.
    - Infections induce chronic inflammation, progressive bronchial wall damage, and dilation.
    - Chronic inflammation

Varicose bronchiectasis

- There is great degree of dilation. Local constrictions cause an irregularity of outline resembling that of varicose veins.

Saccular (cystic) bronchiectasis

- Bronchial dilation progresses and results in ballooning of bronchi that end in fluid-or mucus-filled sacs.

Clinical findings

- Cough and production of copious purulent sputum is common.
- Hemoptysis or and fever is seen.
- Anorexia and poor weight gain may occur.
- Physical examination reveals crackles localized to the affected area.
- Wheezing and digital clubbing may also occur.
- In severe cases, there is dyspnea and hypoxemia.
- Pulmonary function studies may show obstructive, restrictive, or mixed pattern.

Diagnosis

- Associated conditions with bronchiectasis should be diagnosed by appropriate investigations (e.g. sweat test, immunologic workup).
- Chest radiographs in bronchiectasis may be nonspecific. Typical findings include:
    - Increase in size and loss of definition of bronchovascular markings
    - Crowding of bronchi
    - Loss of lung volume
    - Cystic spaces, occasionally with air–fluid levels and honeycombing
    - Compensatory over inflation
    - High resolution CT
- HRCT scan provides:
    - Information on disease location
    - Presence of mediastinal lesions
    - The extent of segmental involvement

Management

- Main treatment for patients with bronchiectasis is medical.
- Aims of treatment are to:
    - Decrease airway obstruction
    - Control infection
- Chest physiotherapy (postural drainage) is very important step of management.
- Parenteral antibiotics are given for 2-4 weeks. Antibiotic choice depends on the identification and sensitivity of organisms found on sputum or bronchoalveolar lavage fluid cultures.
- The most common organisms causing bronchiectasis are *Streptococcus pneumonia*, *Haemophilusinfluenzae*non-type b, *Moraxella catarrhalis*, and *Mycoplasma pneumonia*.
- Amoxicillin/clavulanic acid (22.5 mg/kg/dose twice daily) is initially given.
- Oral (macrolide) or nebulized antibiotics are given according to the severity of the disease.
- Airway hydration (inhaled hypertonic saline or mannitol) liquefy the secretions and help to clear the airways.
- Treatment of any underlying disorder (immunodeficiency, aspiration) is also considered.
- If medical treatment is not effective, segmental or lobar resection may be effective.
- Lung transplantation is the ultimate treatment.

Prognosis

- Earlier recognition or prevention of predisposing conditions leads to good outcome.
- Broad spectrum antibiotics and surgical interventions also decrease morbidity and mortality.
- Long term complication includes stunted growth osteopenia, and osteoporosis.

PULMONARY ABSCESS

- Lung infection if destroys the lung parenchyma, causes cavitations and central necrosis. This results in lung abscesses (localized areas of thick-walled purulent material).
- Lung abscess may be solitary, multiple or secondary to some underlying or predisposing condition.
- Lung abscesses are much less common in children than in adults.

Predisposing conditions

- Aspiration of infected material
- Pneumonia
- Cystic fibrosis
- Gastroesophageal reflux
- Tracheoesophageal fistula
- Immunodeficiencies
- Postoperative complications of tonsillectomy and adenoidectomy
- Seizures
- Many neurologic diseases
- Conditions associated with impaired mucociliarydefense

Pathology and pathogenesis

- Inflammatory vascular obstruction occurs leading to tissue necrosis, liquefaction, and abscess formation.
- Abscess may be a result of pneumonia or hematogenous seeding from another site.
- If the cause is aspiration, right and left upper lobes and apical segment of the right lower lobes are the most affected areas.

Clinical findings

- The most common symptoms are cough, fever, tachypnea, dyspnea, chest pain, vomiting, sputum production, weight loss, and hemoptysis.
- On physical examination, there may be tachypnea, dyspnea, and retractions with accessory muscle use, decreased breath sounds, and dullness to percussion in the affected area.

Diagnosis

- Chest radiography shows:
  - A parenchymal inflammation with a cavity containing an air–fluid level
- Chest CT scan shows:
  - Better anatomic definition of an abscess, including location and size
  - An abscess which is usually a thick-walled lesion with a low-density center progressing to an air–fluid level
- Gram stain of sputum

Management

- Parenteral antibiotics are given for 2–3 weeks in uncomplicated cases, followed by a course of oral antibiotics to complete a total of 4–6 weeks.
- Antibiotics are selected on the results of Gram stain and culture.
- Initially, antibiotics should have aerobic and anaerobic coverage.
  - Penicillinase-resistant agent (active against *S. aureus*)
  - Clindamycin or ticarcillin/clavulanic acid (anaerobic coverage)
  - Aminoglycoside (Gram-negative coverage)
- Large and difficult to treat abscesses are managed with early CT-guided percutaneous aspiration or drainage.

Prognosis

- Prognosis for primary pulmonary abscesses is excellent.
- Abscess due to aerobic organisms may be a negative prognostic indicator.
- Most children become symptom free within 7–10 days. Fever can persist for as long as 3 weeks.
- Abnormalities on chest X-ray usually resolve in 1–3 months but can persist for many months.

PNEUMOTHORAX

CASE

A 5-year-old boy presents with cough, fever, and mild hypoxia. On chest X-ray, he has a ***right upper lobe consolidation***. Suddenly, his condition worsens. He develops ***marked increase in work of breathing*** and ***increasing oxygen requirement***.

Definition

- Pneumothorax is defined as accumulation of extra-pulmonary air within the chest.

Etiology

- Pneumothorax most often results from leakage of air from within the lung. Pneumothorax may occur in pneumonia (usually associated with empyema). It may be also secondary to pulmonary abscess, gangrene, infarct, external chest trauma, foreign bodies in the lung, or rupture of a cyst or an emphysematous bleb as in asthma.
- The two chief causes of spontaneous pneumothorax are:
  - Rupture of a subpleural emphysematous bulla or pleural bleb, or of the pulmonary end of a pleural adhesion.
  - Rupture of a sub-pleural tuberculous focus into the pleural space.

Pathology

- There are three types of spontaneous pneumothorax.
  - **Closed:** As the lung deflates, the communication between pleura and lungs seals off and does not re-open.

  - **Open:** The communication is between pleura and a bronchus (bronchopleural fistula). It does not seal off when the lung deflates. The lung cannot expand because the air pressure in the pleural space is equal to the atmospheric pressure both on inspiration and expiration.
  - **Tension (valvular):** The communication between pleura and lung acts as a one-way valve. Air enters the pleural space during inspiration and coughing but cannot escapes. Intra-pleural pressure may rise above atmospheric levels causing compression of the lung and mediastinal displacement towards the opposite side.

Clinical findings

- Clinical manifestations vary from asymptomatic to severe respiratory distress.
- Onset is usually sudden. There may be respiratory distress, retractions, and markedly decreased breath sounds over the involved lung. There may be pain or a feeling of tightness on the affected side of the chest. Deep breathing may aggravate pain.
- Gradually, the patient becomes breathless and in severe cases may be cyanosed. When the pneumothorax is small and localized, there may be no abnormal signs; but in large pneumothorax, there are signs of air in the pleural space (decreased breath sounds and hyperresonance on the affected side with tracheal deviation to the opposite side). When fluid is present, there is usually a sharply limited area of tympany above a level of flatness to percussion.
- Cardiac function may be compromised when pneumothorax is under tension. There may be hypotension or narrowing of the pulse pressure.

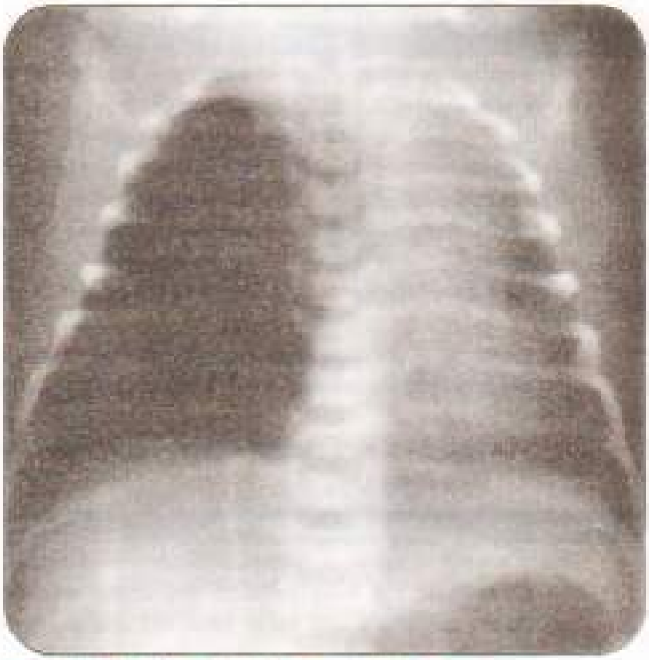


Figure 11.16: Right-sided Pneumothorax

Radiological examination

- Chest X-ray shows the presence of free air in the pleural space.
- If the pneumothorax is large and under tension, there is collapse of the underlying lung and shift of the mediastinum to the opposite side.
- X-ray also shows the presence or absence of pleural fluid and underlying pulmonary disease.

Differential diagnosis

- Diaphragmatic hernia
- Lung cysts
- Congenital lobar emphysema
- Cystic adenomatoid malformation

Management

- Small or asymptomatic peumothoraces usually do not require treatment and can be managed with close observation. A small or even moderate-sized pneumothorax in an otherwise normal child may resolve without specific treatment (usually within about 1 week).
- Larger or symptomatic pneumothoraces usually require drainage. In such a case, inhalation of 100% oxygen to wash out blood nitrogen can be tried.
- Needle aspiration may be followed by chest tube placement (closed thoracotomy).
- Pleural pain needs analgesic treatment.
- Treatment of the underlying pulmonary disease should also be given.
- In older children with spontaneous pneumothorax, recurrences are common and in such a case sclerosing and surgical procedures are needed.

ASTHMA

CASE

A 6-year-old boy has a past history of ***eczema***. His father has chronic rhinitis. Boy has recurrent history of ***cough***, ***wheeze*** and ***breathlessness***. Attack is precipitated by viral infection, exercise, emotion and colder weather. These ***symptoms occur several times a week***.

Definition

- Asthma is defined as reversible obstruction of large and small airways due to hyperresponsiveness to various immunologic and non-immunologic stimuli.

Epidemiology

- Asthma is a common chronic lung disease of children.
- Asthma may have its onset at any age. Before puberty, twice as many boys as girls are affected, but at puberty the sex incidence is equal.
- Asthma is more severe in young children because they are more prone to viral infections (i.e. colds) and

because the proportionately smaller airway size increases airway resistance.

Asthma triggers

- Respiratory infections (viral, mycoplasma)
- Irritants (air pollution, cold air, cigarette smoke)
- Exercise
- Inhaled (dust mite)
- Ingested allergens
- Changes in weather
- Emotional stress
- Medications (aspirin)
- Gastroesophageal reflux
- Sinusitis

Risk factors for the occurrence of asthma

- Poverty
- Small home size (<eight rooms)
- Large family size (≥six members)
- Intense allergenic exposure in infancy (more than 10 mg of house dust mite allergen *Dermotophogoidespteronyssinus* per gram of dust collected from homes)
- Frequent respiratory infections in early childhood

Types of childhood asthma

Recurrent wheezing

- Occurs in early childhood
- Primarily triggered by common respiratory viral infections
- Usually resolves during the 4–5 years of life

Chronic asthma

- It is associated with allergy
- It persists into later childhood (or adulthood)

Pathophysiology

- Asthma is primarily an inflammatory condition of the lungs. Bronchospasm is secondary to inflammation.
- Every asthma attack has these pathologic components:
  - Bronchospasm (bronchoconstriction or smooth muscle contraction)
  - Mucus production
  - Edema and inflammation of the airways mucosa.
  - Infiltration of inflammatory cells (eosinophils, neutrophils, basophils, macrophages)
  - Desquamation of epithelial and inflammatory cells
- The components that predominate at any one time during an attack vary.
- Obstruction occurs during expiration as the airway approaches the closing volume and results in distal airway gas trapping; more severe asthma may have diminished airflow even during inspiration.
- Increased intrathoracic pressure due to hyperinflation may interfere with venous return and reduce cardiac output, which may be manifested as a pulsusparadoxus.
- Mismatching of ventilation with perfusion causes hypoxia which interferes with conversion of lactic acid to carbon dioxide and water, causing metabolic acidosis.Hypercapnia increases carbonic acid, which dissociates into hydrogen ions and bicarbonate ions, causing respiratory acidosis.
- In patients of asthma, an allergic-type of inflammatory response occurs in the airways mucosa that results in bronchial hyperreactivity, the characteristic feature of asthma.
- Risk for development of asthma is associated with elevated serum IgE levels. Following the stimulation or binding of allergens to specific mast cell-associated IgE, there is release of newly synthesized and stored mediators from local mucosal mast cells. These mediators include histamine, leukotrienes C4, D4, and E4, and platelet-activating factor. These initiate bronchoconstriction, mucosal edema, and immune responses.
- **Early immune response** results in bronchoconstriction. It is treatable with B_2-receptor agonists. It can be prevented by mast cell-stabilizing agents (cromolyn or nedocromil).
- **Late phase reaction** occurs 6–8 hours later, and produces a continued state of airway hyperresponsiveness with eosinophilic and neutrophilic infiltration. It can be treated and prevented with steroids. It can also be prevented by mast cell-stabilizing agents.

Clinical findings

- Wheezing is the most characteristic sign of asthma.
- Patient may also have cough, shortness of breath (dyspnea or chest congestion), tachypnea, and exercise intolerance.
- Persistent cough (cough-variant asthma), night cough, exercise induced cough, posttussive emesis, and cough following cold air exposure are also suggestive of asthma.
- Because airway patency decreases at night, many children have acute asthma at this time.
- If symptoms are absent or mild, chest auscultation during forced expiration may reveal prolongation of the expiratory phase and wheezing. With severe obstruction, wheeze or rhonchi may not be heard because of poor air movement.
- Flaring of nostrils, intercostal and suprasternal retractions, use of accessory muscles of respiration, hyperinflated and hyperresonant chest are signs of severe obstruction.
- Central cyanosis may be seen due to severe hypoxia.
- Tachycardia and pulsusparadoxis may be present.
- Agitation, lethargy, inability to speak, tripod sitting position, or diaphoresis are early signs of respiratory failure. Child may sit with arms supported in front on the pillows to support the chest and facilitate the use of accessory muscles of respiration.

Table 11.4: Formal evaluation of asthma exacerbation severity in the urgent or emergency care setting

	Mild	**Moderate**	**Severe**	**Subset: Respiratory Arrest Imminent**
Symptoms				
Breathlessness	While waling	While at rest (infant—softer, shoter cry, difficulty feeding)	While at rest (infant—stops feeding)	
	Can lie down	Prefers sitting	Sits upright	
Talks in	Sentences	Phrases	Words	
Alertness	May be agitated	Usually agitated	Usually agitated	Drowsy of confused
Signs				
Respiratory rate[*]	Increased	Increased	Often >30 breaths/minute	
Use of accessory muscles; suprasternal retractions	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Wheeze	Moderate; often only end-expiratory	Loud; throughout exhalation	Usually loud; throughout inhalation and exhalation	Absence of wheeze
Pulse rate (beats/minute)[†]	<100	100–200	>120	Bradycardia
Pulsusparadoxus	Absent	May be present	Often present	Absence suggests respiratory muscle fatigue
	<100 mmHg	10–25 mmHg	>25 mmHg (adult)	
			20–40 mmHg (child)	
Functional assessment				
Peak expiratory flow (value preicted or personal best)	≥70%	Approx. 40–69% or response lasts <2 hr	<40%	<25%[‡]
PaO_2 (breathing air)	Normal (test not usually necessary)	≥60 mmHg (test not usually necessary)	<60 mmHg; possible cyanosis	
and/or				
PaO_2	<42 mmHg (test not usually necessary)	≤42 mmHg (test not usually necessary)	>42 mmHg; possible respiratory failure	
SaO_2 (breathing air) at sea level	>95% (test not usually necessary)	90–95% (test not usually necessary)	<90%	
	Hypercapnia (hypoventilation) develops more readily in young children than in adults and adolescents			

- Between attacks child may be entirely free of symptoms. But children with chronic asthma are below average for height and weight. The chest tends to be barrel-shaped with an increase in anteroposterior diameter. The sternum may become prominent and there is development of Harrison's sulci.

Diagnosis

- Diagnosis is mainly clinical.
- **Blood examination:** In case of respiratory infection, CBC is helpful. Leukocytosis is common in acute severe asthma without evidence of bacterial infection. There may be eosinophilia. There may be raised level of IgE in the blood.
- There may be **sputum** eosinophilia.
- **Chest X-ray:** It shows:
  - Hyperinflated and hyperlucent lungs.
  - Increased anteroposterior diameter of chest (increased retrosternal space on lateral X-ray).
  - Flattening of diaphragm,
  - More horizontal ribs
  - Heart appears narrow and elongated
- **Arterial blood gases:** Hypoxemia results from airway obstruction, and arterial PO_2 continues to drop as the attack occurs. Initially, because of hyperventilation, arterial PCO_2 is low. During severe attack, PCO_2 will subsequently rise (respiratory acidosis) as hypoventilation and respiratory failure occurs.
- **RAST test:** In case of chronic asthma, skin test and Radioallergosorbent Testing (RAST) are useful in identification of environmental triggers.
- **Pulmonary function tests:**
  - Peak Expiratory Flow Rate (PEFR) decreased.
  - Vital Capacity (VC) reduced.
  - Forced Expiratory Volume in one second (FEV_1) decreased.
  - The Residual Volume (RV), Functional Residual Capacity (FRC), and Total Lung Capacity (TLC) increased.

(Reversal or significant improvement of these abnormalities in response to inhaled bronchodilator therapy alone or with anti-inflammatory therapy is observed in asthma. Diurnal variation in PEFR i.e. the difference between morning and evening measurements of greater than 15–20% has been used as a defining feature of asthma).

Differential diagnosis

- Wheezy bronchitis: Croup, acute bronchiolitis, pneumonia, pertussis
- Foreign body in the airway
- Endobronchial tuberculosis or lymph node pressing the bronchi
- Cystic fibrosis
- Congenital malformations such as vascular ring
- Cardiac asthma

Complications

- Pneumothorax, pneumomediastinum
- Delayed maturation and slowing of pubertal growth velocity

MANAGEMENT OF ACUTE ASTHMA ATTACK

- **Oxygen** is administered (2–3 L/minute) by mask or nasal prongs.
- **Nebulized salbutamol** (a □-agonist) is used as a first line therapy and is safe and effective at a dose of 0.5 mg/kg/dose followed by 0.1–0.5 mg/kg/dose at intervals of 20–30 minutes until adequate response is achieved. Salbutamol is available as a 0.5% solution (5 mg/ml) to be diluted with 1.5 ml normal saline. Nebulization with oxygen at 6 L/minute prevents salbutamol-induced hypoxemia. Hold or decrease dose for heart rate >180/minute. If acute attack is controlled, oral salbutamol (0.2–0.4 mg/kg/day) or inhaled salbutamol (200 mg or 2 puffs) is given every 6 hourly. Adverse effects are tachycardia, arrhythmias, CNS stimulation, hyperactivity, hypokalemia, and irritability.
- **Adrenaline** is not used routinely. When used, a dose of 0.01 ml/kg (1:1000 solution) may be given subcutaneously. It may be necessary to repeat the same dose once or twice at intervals of 20 minutes to obtain optimal relief. In infants and small children, a dose of 0.05 ml is often effective. If the patient is still in distress after 3 doses, do not give further doses. It should not be given if heart rate is above 180/minute in infants and 160/minute in older children. Side effects of adrenaline are pallor, tremors, anxiety, palpitations, headache, and serious arrhythmias. These side effects are minimized if doses of no more than 0.3 ml are given at any age.

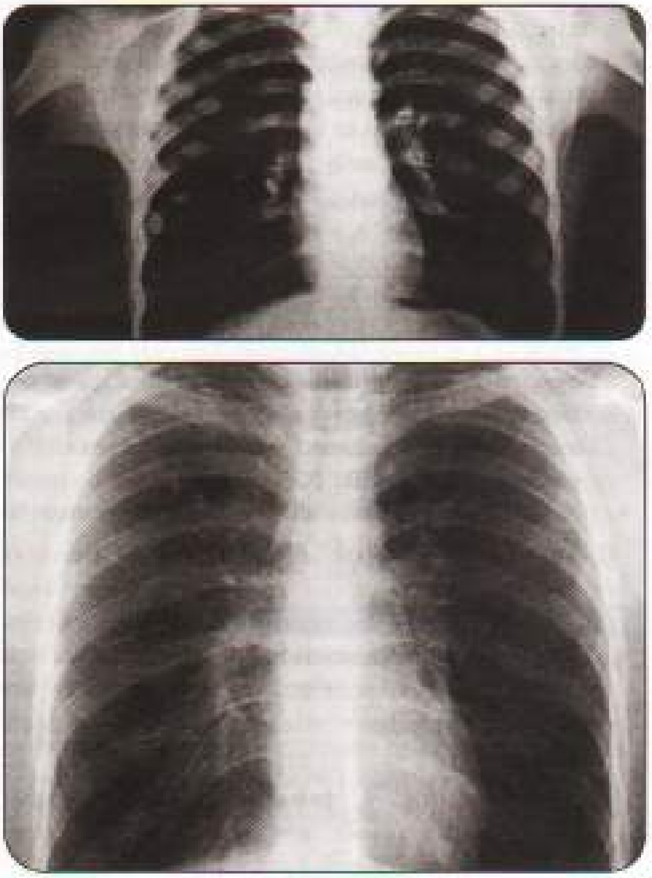


Figure 11.17: X-ray chest in a patient with asthma showing hyperinflation.

- **Terbutaline**, a more selective β_2-agonist is available in injectable form and is an alternative to adrenaline. Dose is 0.01 ml/kg/dose (1:1000 solution). The duration of action is up to 4 hours. The maximal dose of terbutaline by subcutaneous injection is 0.25 ml. If necessary, this dose may be repeated once, after 20 minutes.
    - **Aminophylline** does not provide additional benefit for patients receiving optimal treatment with an inhaled agonist but should be considered:
    - For patients who have been receiving maintenance treatment with theophylline.
    - For those unable to tolerate maximal treatment with inhaled β_2-agonists.

  Aminophylline is given in a dose of 5 mg/kg intravenous slow diluted for 5–15 minutes at rate no greater than 25 mg/minute. This dose is not given if the patient has already received theophylline in the past few hours, until the blood level of theophylline is known. The dose can be repeated at 6–8 hours intervals and total daily dose should not exceed 20 mg/kg. It can be given for few days till the acute stage is over. Rapid intravenous infusion of aminophylline can lead to cardiac arrhythmias, hypotension and death.
- **Hydrocortisone** is given to prevent late phase reaction. IV dose is 5–10 mg/kg every 4–6 hours till improvement is evident and can be followed by an oral steroid (prednisolone 1 mg/kg/day for 5 days) or inhaled steroid (beclomethasone 500 mg or 2 puffs twice daily). Nebulized steroids are also effective. Steroids can be started initially if the child has received steroids previously or is on long-term steroid.
- **Adequate hydration:** Dehydration may be present, due to inadequate fluid intake, greatly increased insensible water loss as a result of tachypnea, and the diuretic effect of theophylline. Give 20 ml/kg of normal saline over a period of 1–2 hours and then continue fluids at 1 ½ times the maintenance rate for next 1–2 days. Circulatory overload and pulmonary edema should be avoided. Because β_2-agonists may produce hypokalemia, potassium should be added to the intravenous fluids after patient voids.
- **Antibiotics:** If bacterial infection is suspected, appropriate antibiotics are given.
- **Ventilatory support** may be required.

Subsequent management

- Following a severe episode of acute asthma, small airways obstruction may persist for 2 months or longer.
- So oral or inhaled pharmacologic therapy (salbutamol, steroids, theophylline) should be continued for several weeks or months depending on the chronicity of the illness.

MANAGEMENT OF STATUS ASTHMATICUS

- If a patient continues to have significant respiratory distress despite administration of sympathomimetic drugs with or without theophylline, the diagnosis of status asthmaticus should be considered.
- Status asthmaticus is a clinical diagnosis defined by increasingly severe asthma that is not responsive to drugs that are usually effective.
- A patient with status asthmaticus should be admitted to an intensive care unit, where the condition can be carefully monitored. Complete blood count, serum electrolytes, arterial blood gases, and cardiac status should be monitored.
- To prevent hypoxia, oxygen (2–3 L/minute) is given to maintain a partial pressure of arterial oxygen to 70–90 mmHg or oxygen saturation greater than 92%.
- If patient is previously on steroid therapy, steroids are given initially.
- Other stepwise approaches are with salbutamol nebulization, salbutamol + ipratropium nebulization, aminophylline infusion, adequate hydration, or steroids as described in management of acute asthma attack.
- Mechanical ventilation is considered in case of respiratory failure in spite of all the above measures.

LONG-TERM MANAGEMENT OF CHRONIC ASTHMA

In the management of chronic asthma, there are four main components to therapy.

1. Patient education
    - Improving patient skills in use of spacer devices for Metered-Dose Inhalers (MDIs)
    - Use of peak flow monitoring
    - Use of self-management and environmental control measures
    - Information about medications and their side effects
    - When and how to respond to changes in symptoms
2. Assessment and monitoring of asthma severity with objective measurement of lung function
3. Avoidance or control of asthma triggers
4. Establishment of comprehensive plans of pharmacologic therapy, including plans for managing exacerbations

- **Cromolyn** and **nedocromil** inhibit early and late-phase allergen-induced bronchospasm and acute bronchospasm after exercise or cold air; neither is a bronchodilator. Both are useful as prophylactic agents in children with mild to moderate asthma particularly since they have virtually no known side effects.
- Inhaled **Corticosteroids** (ICS) are safe and extremely effective therapy for chronic asthma. Inhaled corticosteroids reduce airway hyperreactivity and reduce the need for rescue broncho-dilator therapy. Long-term oral use of corticosteroids should be reserved for chronic asthma only if other therapies fail;

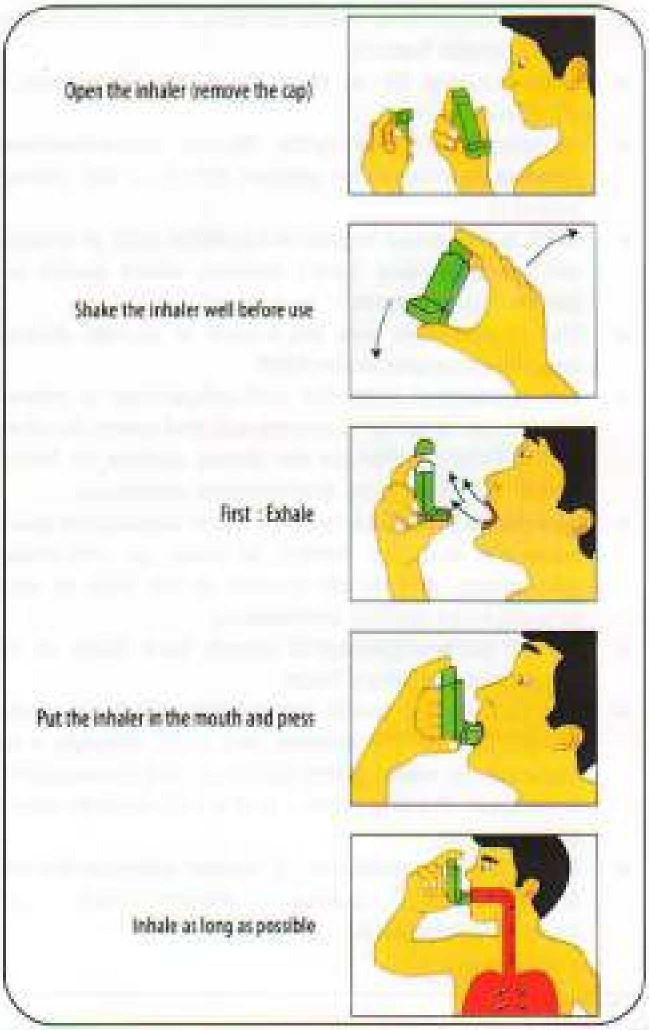

Open the inhaler (remove the cap)
Shake the inhaler well before use
First : Exhale
Put the inhaler in the mouth and press
Inhale as long as possible

Figure 11.18: Method to use an inhaler.

such use is preferable with an alternate-day schedule, which may reduce side effects. The side effects associated with short courses (<7 days) of oral corticosteroids are significantly less than those associated with long-term use. Short courses of oral corticosteroids are beneficial in minimizing acute exacerbation in moderate to severe asthma. It is recommended that daily ICS therapy is the treatment of choice for all patients with persistent asthma.

- **β_2-adrenergic agonists** are useful for the treatment of both acute and chronic asthma, but they alone do not give long-term control because they do not affect airway inflammation. They relax airway smooth muscle, enhance mucociliary clearance, and may decrease mediator release from mast cells and basophils.
    - **Short-acting inhaled beta$_2$-agonists (e.g. salbutamol)** are beneficial for acute exacerbations of asthma, for the pre-treatment of exercise-induced asthma, and for rescue (quick-relief) therapy in the treatment of chronic asthma.
    - **Long-acting inhaled beta$_2$-agonists** have a duration of action more than 12 hours and are useful for treating chronic asthma that is unresponsive to inhaled anti-inflammatory agents and for treating night-time cough. These must not be used for acute exacerbations.
- Sustained-release theophylline is a bronchodilator with mild anti-inflammatory effects.
- **Anti-cholinergic agents**, such as ipratropium are potent bronchodilator that may also block reflex bronchoconstriction caused by inhaled irritants. They are less effective as bronchodilators than β_2-agonists for the treatment of asthma but may be useful when nebulized together with β_2-agonists.

- **Leukotriene antagonists** (Zafirlukast is an oral leukotriene D4 receptor antagonist) and **lipoxigenase inhibitors** (Zileuton) are anti-inflammatory agents but are not bronchodilators. Montelucast tablet is given (for 2–5 years 4 mg daily; for 6–14 years 5 mg daily; for >15 years 10 mg daily).
- **Anti-Immunoglobulin E** is a humanized monoclonal antibody. It binds IgE and blocks IgE-mediated allergic responses and inflammation. It is given every 2–4 weeks subcutaneously.

Prognosis

- The prognosis for asthma is generally good provided that aggressive therapy is instituted early.
- Death is rare and is almost always a result of under-treatment.
- Ultimate remission depends partly on growth in the cross-sectional diameter of the airways. About 50% of all asthmatic children are virtually free of symptoms within 10–20 years, and only 5% experience severe disease. Recurrence may occur in adulthood.
- Resolution is rare in children with severe asthma characterized by chronic steroid-dependent disease with frequent hospitalization; about 95% become asthmatic adults.

Prevention

- The primary prevention for asthma is to reduce the risk of developing allergies and asthma initially.
- Breastfeeding (>4 months) reduces wheezing episodes. The benefits of breastfeeding persist throughout the first 6 years of life. Breastfeeding is especially useful in reducing asthma symptoms in children exposed to tobacco smoke.
- Once a child is known to be at risk for repeated asthmatic attacks, prevention is aimed at reducing triggers.
- All standard childhood immunizations are recommended for children with asthma, including varicella and annual influenza vaccines.

CYSTIC FIBROSIS

CASE

A 5-year-old child presents with a history of ***poor growth*** (failure to gain weight), ***fatty stools***, nasal polyps, ***chronic cough***, and frequent pulmonary infections. He also has digital clubbing and rectal prolapse. ***Sweat test*** shows ***elevated chloride concentration***. DNA testing show that the boy is homozygous for the cystic fibrosis mutation known as F508.

Definition

- Cystic Fibrosis (CF) is an inherited multisystem disorder of children and adults.
- CF is the major cause of severe chronic lung disease and is responsible for most common exocrine pancreatic insufficiency during early life.
- CF is also responsible for:
  - Hyponatremic salt depletion
  - Nasal polyposis
  - Pansinusitis
  - Rectal prolapse
  - Pancreatitis
  - Cholelithiasis
  - Nonautoimmune insulin-dependent hyperglycemia

Pathogenesis

- CF is inherited as an autosomal recessive trait.
- A dysfunction of epithelial surfaces is the predominant pathogenetic feature.
- Gene causing CF is located on the long arm of chromosome 7.
- Dysfunction of the cystic fibrosis transmembrane conductance regulator protein (CFTR) is the primary defect in CF.
- CFTR is expressed largely in epithelial cells of airways, GIT (pancreas and biliary system), sweat glands and genitourinary system.
- The CF epithelial cells are unable to secrete chloride ions (Cl-) in response to cAMP.
- The postulated epithelial pathophysiology in airways involves an inability to secrete salt and water. So, there is insufficient water on the airway surface to form a pericilliary liquid layer and hydrated secretions.
- Desiccated secretions become more viscous and elastic (rubbery) and are harder to clear by mucociliary mechanism. Airflow obstruction at the level of small airways is the earliest abnormality.
- Similar pathophysiological events take place in the pancreatic and biliary ducts.
- The function of sweat gland duct cells is to absorb rather than secrete chloride. But in CF, chloride is not absorbed by sweat gland duct cells and is transported in sweat to the skin surface that is why chloride level is high in sweat.
- There is high prevalence of airway colonization with Staphylococcus aureus, Pseudomonas, and Burkholderiacepacia.

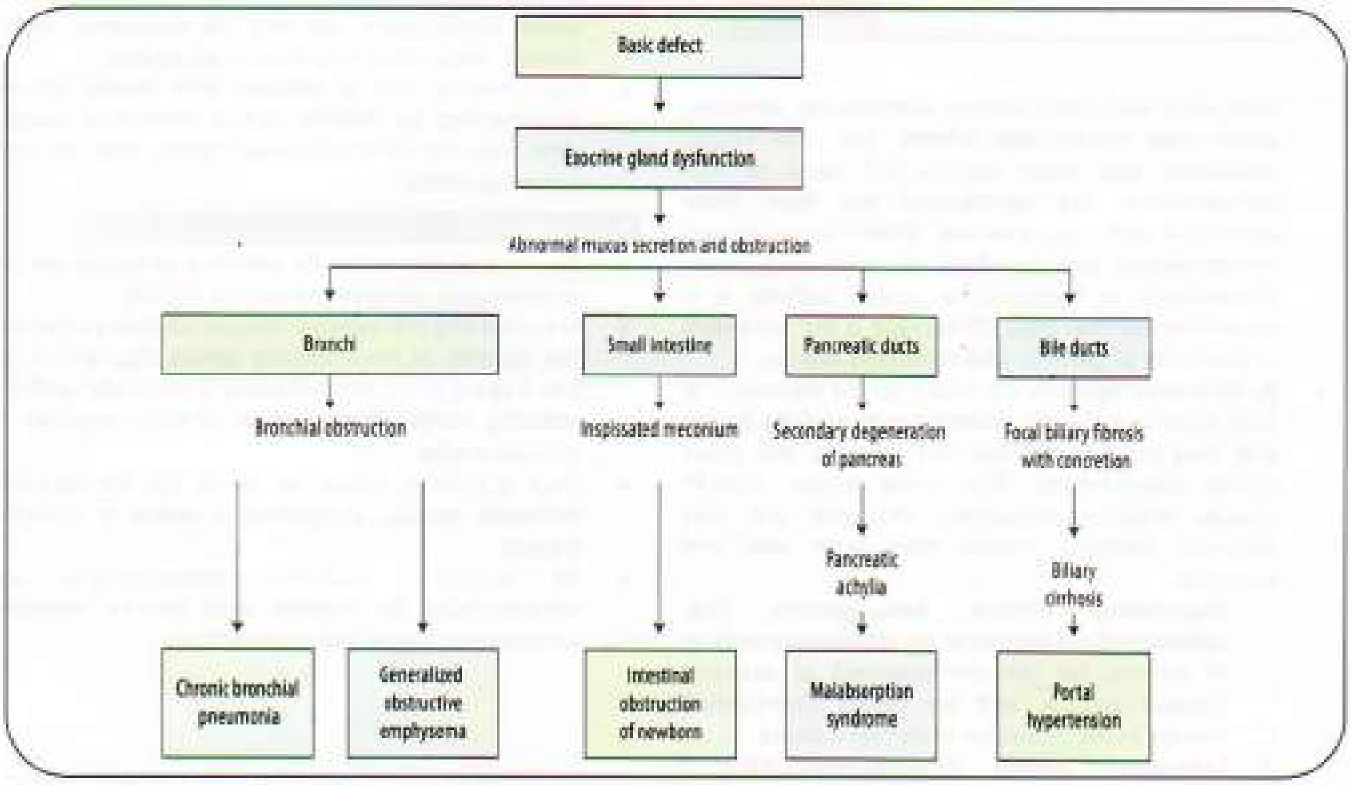

Basic defect
Exocrine gland dysfunction
Abnormal mucus secretion and obstraction
Branchi
Small intestine
Pancreatic ducts
Bile ducts
Bronchial obstruction
Inspissated meconium
Secondary degeneration of pancreas
Focal biliary fibrosis with concretion
Pancreatic achylia
Biliary cirrhosis
Chronic bronchial pneumonia
Generalized obstructive emphysema
Intestinal obstruction of newborn
Malabsorption syndrome
Portal hypertension

Figure 11.20: Various effects of exocrine gland dysfunction in cystic fibrosis.

Clinical findings

Respiratory tract

Respiratory insufficiency is caused by abnormal mucous gland secretion causing:

- Cough initially dry but later on productive (purulent sputum)
- Exercise intolerance
- Dyspnea
- Expiratory wheeze
- Increased AP diameter of chest
- Generalized hyperresonance
- Coarse crackles
- Digital clubbing
- Cyanosis

Intestinal tract

- In 15–20% of newborns with CF, there is meconium ileus. There is abdominal distension, emesis and failure to pass meconium within first 48 hours of life.
- Maldigestion from exocrine pancreatic insufficiency occurs in more than 85% of patients:
    - Frequent, bulky greasy stools
    - Fat soluble vitamin (A, D, E, K) deficiencies
    - Failure to gain weight, retarded growth

Biliary tract

- Biliary cirrhosis becomes symptomatic in 2–3% of patients:
    - Icterus
    - Ascites
    - Hematemesis

Sweat glands

- Excessive loss of salt in the sweat predisposes to salt depletion episodes (especially during episodes of gastroenteritis and during warm weather).
- There is hypochloremic alkalosis.
- Hyponatremia is a risk particularly in warm season.

Complications

- Concentrations of electrolytes (sodium and chloride) in sweat are abnormally high in all patients. This causes:
    - Hyponatremia
    - Hypochloremic metabolic alkalosis
- Hemoptysis
- Pneumothorax
- Corpulmonale
- Meconium ileus (abnormally viscid meconium completely obstructs the ileum)
- Rectal prolapse
- Congenital obliteration of the vas deferens (all males who have cystic fibrosis are sterile)
- Females have reduced fertility due to thick, spermicidal cervical mucus
- Focal biliary cirrhosis
- Abnormal glucose tolerance. Type II diabetes
- Chronic sinusitis
- Nasal polyposis

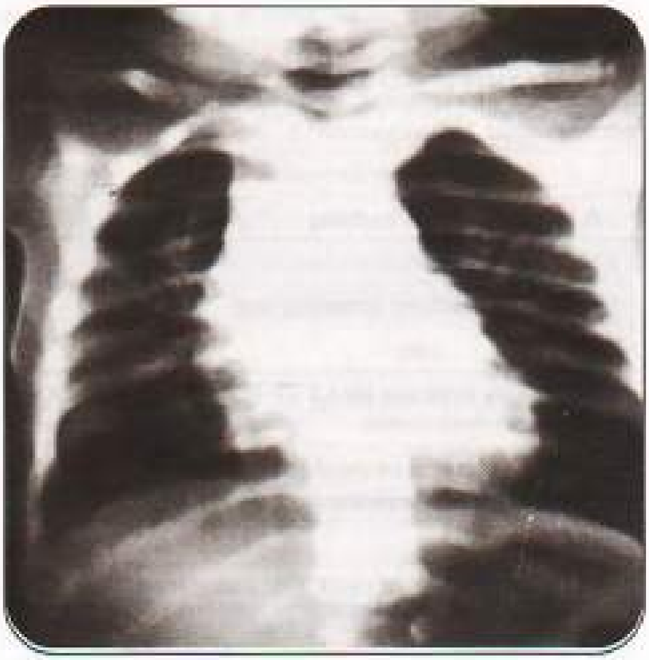
- Diagnosis
- Sweat test
- The sweat test is the standard approach to diagnosis of CF
- It involves using pilocarpineiontophoresis to collect sweat and performing chemical analysis of its chloride content.
- A 3-mA electric current is used to carry pilocarpine into skin of forearm and locally stimulate the sweat glands. Sweat is collected on filter paper. After 30–60 minutes, filter paper is removed, weighed and eluted in distilled water. A chloridometer is used for analysis of chloride in the sample.
- It is positive if the chloride concentration of sweat exceeds 60mEq/L. Normal sweat chloride values are below 40mEq/L.
- Testing may be difficult in the first 2 weeks of life because of low sweat rates but is recommended any time after the first 48 hours of life. Positive results should be confirmed. For a negative result, the test should be repeated if suspicion of the diagnosis remains.

Pancreatic function

- Measurement of fat balance in a 3-day stool collection
- Quantitation of trypsin and chymotrypsin activity in fresh stool sample is a useful screening test
- Serum immunoreactivetrypsinogen level

Chest X-ray

- There is evidence of bronchiectasis and prominent hilar lymph nodes.



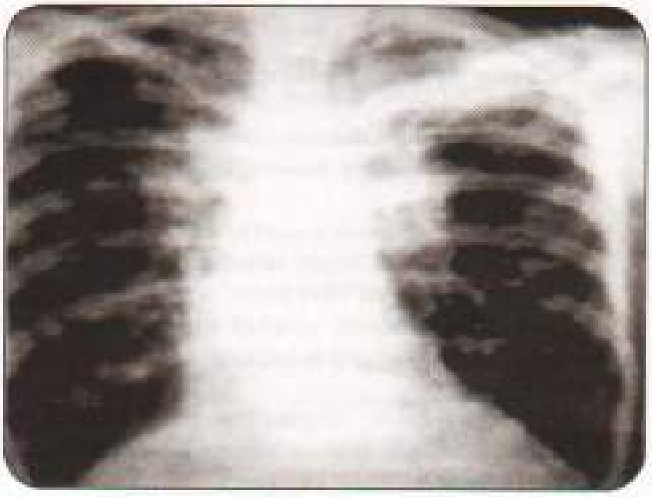


Figure 11.21: X-ray chest in a patient with cystic fibrosis.

Microbiology

- Culture of lower airways secretions (e.g. sputum)
- The finding of Staph.Aureus or P. aeruginosa strongly suggests a diagnosis of CF.

DNA testing

- This is the test of the most common *CFTR* mutations.
- This test identifies ≥90% of carriers who carry 2 CF mutations.

Other diagnostic tests

- The finding of increased potential differences across nasal epithelium (nasal potential difference).
- Pre-natal DNA testing: It is offered to all families with a history of cystic fibrosis.
- Evidence of meconium ileus: It is diagnostic of cystic fibrosis if:
  - Failure to pass a stool in the first 24 hours of life
  - Small bowel obstruction (usually in the area of ileocecal valve)
  - Evidence of a micro-colon

Table 11.5: Diagnostic Criteria for Cystic fibrosis (CF).

Presence of typical clinical features (respiratory, gastrointestinal, or genitourinary)
or
• A history of CF in a sibling
or
• A positive newborn screening test
plus
• Laboratory evidence for CFTR (CF transmembrane regulator) dysfunction:
○ Two elevated sweat chloride concentrations obtained on separate days
or
○ Identification of two CF mutations
or
○ An abnormal nasal potential difference measurement

Table 11.6: Conditions associated with false-positive and false-negative sweat test results

With false-positive results:
• Eczema (atopic dermatitis) • Ectodermal dysplasia • Malnutrition • Anorexia nervosa • Congenital adrenal hyperplasia • Adrenal insufficiency • Glucose-6-phosphatase deficiency • Familial hypoparathyroidism • Hypothyroidism • Nephrogenic diabetes insipidus • Pseudohypoaldosteronism • Klinefelter syndrome
With False-Negative Results:
• Dilution • Malnutrition • Edema • Insufficient sweat quantity • Hyponatremia • Cystic fibrosis transmembrane conductance regulator mutations with preserved sweat duct function

Management

Supportive care

- Clearing of pulmonary involvement
- Education of the patient and parents
- Follow-up evaluations every 1–3 months
- Secretions of CF patients should be adequately hydrated (oral hydration, especially during warm weather or with acute gastroenteritis). Intravenous therapy for dehydration, if needed, should be initiated early.
- Goal of therapy is to maintain a stable condition as much as possible for prolonged periods.

Pulmonary therapy

- Pulmonary therapy is needed to clear secretions from airways and to control infection.
- **Antibiotics** are given to prevent and treat pulmonary bacterial infection. Choice of antibiotics depends upon the culture of sputum. The usual course of therapy is 2 weeks or more and maximal doses are recommended.
- **Inhalation therapy**

  - Agents used are bronchodilators, normal saline, cromolyn sodium, or inhaled steroids.
  - 7% hypertonic saline nebulized 2–4 times daily results in increased mucus clearance and improved pulmonary function.
  - Human recombinant–DNase (2.5 mg) in single daily aerosol dose improves pulmonary function.
  - N–acetylcysteine (mucolytic) can be used.
  - Aerosolized antibiotics are used when the airways are colonized with *Pseudomonas*. Common antibiotics used are aerosolized tobramycin, or aerosolized aztreonam.
- Alternate-day **steroids** reduce inflammation and produces improvement in pulmonary function.
- **Chest physiotherapy** is used 2–4 times a day (depending on severity of lung dysfunction) to aid the clearance of viscid secretions. It includes:
  - Breathing exercises
  - Postural drainage with or without chest percussion
- Endoscopy and lavage of obstructed airways.

Nutritional therapy

- Patients with CF have loss of exocrine pancreatic function resulting in inadequate digestion and absorption of fats and proteins.
- Nutritional therapy includes:
  - Dietary adjustment
  - Pancreatic enzyme replacement
  - Supplementary vitamins
- Children with CF need excessive daily calories than usual to grow.
- Daily supplements of the fat-soluble vitamins are required.
- Weight gain sometimes requires nocturnal feeding via nasogastric tube or percutaneous enterostomy or with short-term intravenous hyperalimentation.

Other therapies

- Recombinant growth hormone therapy (3 times per week) improves height and weight velocities.
- **Pancreatic enzyme replacement therapy** is given to improve digestive function. This contains lipase 2000-4000IU per feeding, amylase, and protease. Lipase should not exceed 2500IU/kg/meal. Excessive doses cause colonic strictures.
- **High-calorie, high-protein diet** should be provided.
- **Fat soluble vitamins (A, D, E, and K)**supplementation is given.
- Minerals especially zinc is needed to prevent acrodermatitisenteropathica. Iron is also needed.
- **Stool softeners** are given
- **Surgery for meconium ileus**
- **Lung transplantation**
- **Gene therapy**
- **Adenosine triphosphate-uridine triphosphate:** It increases chloride secretion in cystic fibrosis airways making secretions thinner.
- Ivacaftor is a small molecule potentiator of the CFTR mutation. It activates the CFTR-G551D mutant protein that results in decreased frequency of pulmonary exacerbations, decreased sweat chloride and increased weight gain. It is given to CFTR-G551D patients ≥6-year-old. Dose is 150 mg, twice per day, oral therapy.

Prognosis

- CF remains a life-limiting disease.
- Lung disease has slow progression but eventually reaches to disabling condition.
- With appropriate medical and psychosocial support, children with CF generally have a healthy life approaching a productive adulthood.

CHAPTER 12

Gastrointestinal and Liver Disorders

EVALUATION OF A CHILD WITH VOMITING

Definition

- Vomiting is defined as a coordinated, sequential series of events that leads to forceful oral emptying of gastric contents.
- Vomiting is usually preceded by nausea and is accompanied by forceful gagging and retching.
- Regurgitation, on the other hand, is effortless and not preceded by nausea.
- Evaluation of a child with vomiting needs following points:
    - Complete history
    - Physical examination
    - Description of the vomitus
- History and physical examination are the essential starting points and should include:
    - Duration of vomiting
    - Presence of blood or bile in the vomitus. Bacterial and viral gastroenteritis associated with diarrhea may produce generalized ileus with bilious vomiting. In case of bloody vomitus, it is important to confirm that the material vomited is indeed blood.
    - Presence of abdominal pain or distension. Pain localized to the right lower quadrant suggests appendicitis. In pancreatitis or generalized peritonitis, pain is in midline or diffuse. Abdominal distention suggests intestinal obstruction.
    - The characteristics of the stools
    - Presence of fever

Table 12.1: Causes of bloody vomiting.

Causes of bloody vomiting
• Swallowed maternal blood in the newborn
• Oropharyngeal lesions
• Nose bleed
• Peptic ulcer disease
• Bleeding disorders
• Foreign bodies
• Esophageal varices

Investigations

- An upper gastrointestinal series is needed to rule out anatomic causes. Endoscopy is also helpful.
- Complete blood count, serum electrolytes, and urine examination, are done. Hematocrit should also be measured.

Table 12.2: Causes of vomiting.

GIT disorders:
• Gastroesophageal reflux
• Hypertrophic pyloric stenosis
• Peptic ulcer disease
• Celiac disease
• Hirschsprung's disease
• Appendicitis
• Gastroenteritis
• Inflammatory bowel disease
• Hepatitis
• Peritonitis
• Meconium ileus in newborn
• Intussusception
• Cow's milk protein allergy
• Intestinal obstruction
Extra-GIT disorders:
• Sepsis
• Pneumonia
• Otitis media
• UTI
• Meningitis
• Hydrocephalus
• Brain tumor
• Intoxications
• Inborn errors of metabolism

Complications of vomiting

- Fluid loss in emesis (dehydration)
- Bicarbonate loss (alkalosis, hypochloremia)
- Sodium and potassium loss (hyponatremia, hypokalemia respectively)
- Malnutrition, failure to thrive
- Mallory-Weiss tear (forceful emesis causes hematemesis)
- Esophagitis in chronic vomiting
- Aspiration of vomiting (in children with pneumonia or neurologic dysfunction)
- Shock due to severe fluid loss

Management

- Management of vomiting needs treatment of consequences and cause of vomiting.
- Passage of nasogastric tube will help to determine whether bleeding is ongoing.
- In severe vomiting, cardiovascular stability of the child is essential.

- Dehydration must be treated with fluid resuscitation.
- Electrolyte imbalances should be corrected by appropriate choice of fluids.
- Antiemetic medicationsshould not be prescribed until the etiology of the vomiting is known and in severe cases.
- No antiemetic should be used in patients with surgical emergencies.
- No antiemetic needed when a specific treatment of the underlying condition is possible.
- In viral gastroenteritis, correction of dehydration, ketosis, and acidosis may be helpful to reduce vomiting.

GASTROESOPHAGEAL REFLUX DISEASE

CASE

A 2-month-old girl presents with ***recurrent vomiting*** since birth. There is no blood or bile in the vomiting. Most episodes follow after a feed. She is ***thriving well***. Physical examination is unremarkable.

- Gastroesophageal Reflux (GER) means passage of gastric contents into the lower esophagus.
- Effortless spitting to forceful vomiting after feeding (post-prandial regurgitation) is a common symptom of gastroesophageal reflux in infants. It is usually harmless (physiological gastroesophageal reflux). It is normal in infants younger than 8 to 12 months old.
- Severe gastroesophageal reflux needs treatment. Gastroesophageal Reflux Disease(GERD) occurs when GER leads to severe symptoms or complications such as poor growth, pain, or breathing difficulties.
- Children with asthma, cystic fibrosis, developmental handicaps, hiatal hernia, and repaired tracheoesophageal fistula are at increased risk of GERD.

Pathophysiology

- Nearly half of all infants have gastroesophageal reflux at 2 months of age.
- Factors involved in gastroesophageal reflux include:
  - Liquid diet
  - Supine position
  - Short esophagus.
  - Small non-compliant stomach
  - Frequent large volume feeding
  - Immature Lower Esophageal Sphincter (LES)
- As infant grows, esophagus and stomach become compliant, solid food are introduced in the diet, upright position is attained so reflux stops by 8–12 months of age.
- Transient LES relaxation is the major primary mechanism allowing reflux to occur. Gastric distension, straining, obesity, large volume/hyperosmolar meals and increased respiratory efforts like coughing and wheezing increase reflux episodes.

Difference between GER & GERD

GER	GERD
No evidence of weight loss	Significant weight loss
Not having respiratory symptoms	Respiratory symptoms in form of apnea, cyanosis, aspiration, wheezing or recurrent pneumonia
No signs of esophagitis	Signs of esophagitis like dysphagia, lower chest pain, hematemesis.
No Neurobehavioral symptoms	Neck tilting in infants (Sandifer symptoms)

Clinical findings

- Most common manifestation of gastroesophageal reflux is esophageal disease.
  - Signs of esophagitis like irritability, arching, choking and gagging occur.
  - Failure to thrive.
  - Abdominal and chest pain.
- Extra-esophageal symptoms are age dependent.
  - During infancy, there may be obstructive apnea, stridor or lower airway disease.
  - In older children, airway manifestations are related to asthma, laryngitis, and sinusitis.

Complications

- Common complications of gastroesophageal reflux are:
  - Failure to thrive
  - Esophagitis with hematemesis
  - Occult blood loss
  - Anemia
  - Esophageal stricture
  - Aspiration pneumonia
  - Chronic cough
  - Wheezing
  - Asthma-like attacks
  - Dysphagia
  - Dental erosions
  - Neck contortions, arching, turning of head (Sandifer's syndrome)
  - Apnea (in young infants)
- Gastroesophageal reflux is common in neurologically impaired children.

Diagnosis

- Usually diagnosed clinically. Infant is thriving normally.
- On barium swallow, free regurgitation of barium from stomach to esophagus occurs.
- Upper GIT series may be needed to rule out anatomic causes of vomiting.

- A sensitive test is prolonged monitoring of lower esophageal pH. It will be acidic (pH <4) due to regurgitation of stomach contents.
- Esophageal impedance monitoring records the regurgitation of electrolyte-rich gastric fluid in the esophagus.
- Endoscopy is used to evaluate the esophagitis, esophageal stricture, and anatomic abnormalities.

Management

- Physiological reflux (in otherwise healthy young infant) does not require specific treatment. It is self-limiting in about 85% of cases. It usually disappears between 8–12 months of age.
- Spontaneous resolution is less likely in older children with GERD.

Conservative treatment

- In mild cases, erect posture and initiation of solid feeding will be curative.
- Frequent, small feedings thickened with rice cereal (2–3 TSF/oz of milk).
- Placing the child in prone position and upright carried position with elevated head end of bed.
- Burp more frequently.
- Stick to a regular feeding schedule.
- Keep the baby away from smoke.
- Avoid chocolate and beverages.

Medical treatment

- H_2 receptor antagonists (ranitidine, 3 mg/kg/day in two divided doses)
- Proton pump inhibitors (omeprazole 0.7–3.3 mg/kg/day) before meals
- Prokinetic agents (metoclopramide 0.1 mg/kg before meals) hasten gastric emptying and improve esophageal motor function

Surgical treatment

- Surgery is indicated in:
  - Persistent vomiting with failure to thrive
  - Esophagitis or esophageal stricture
  - Apneic spells or chronic pulmonary disease unresponsive to 2–3 months of medical therapy
- Surgical option is fundoplication (Nissen operation) combined with gastrostomy for feeding

Prognosis

- Prognosis in normal infants is good.
- Less response to medical therapy is noted in:
  - Children over 18 months of age
  - Children with large hiatus hernia
  - Neurologically handicapped children

CHRONIC DIARRHEA

CASE

A 3-year-old child presents with failure to thrive and chronic diarrhea. He passes frequent loose stools per day. There is abdominal distension. There is no fever, jaundice, ascites or hepatosplenomegaly. CBC is normal.

Definition

Diarrhea is the excessive loss of stool water and electrolytes. In infants, stool volume greater than 15 g/kg/day, and in children 200 g/day is considered diarrhea.

Chronic diarrhea is defined as diarrhea, which persists for more than two weeks and usually its etiology is non-infectious.

Pathogenesis

- Diarrhea may result from any of the following pathogenetic mechanisms:
  - Interruption of normal cell transport processes for water, electrolytes, or nutrients.
  - Decrease in the surface area available for absorption (decreased functional capacity), which may be due to shortening of the bowel or mucosal disease. For example short bowel syndrome.
  - Increase in intestinal motility. There is decreased transit time. For example irritable bowel syndrome, thyrotoxicosis.
  - Increase in unabsorbed osmotically active molecules in the intestinal lumen.
  - Increase in intestinal permeability, leading to increased loss of water and electrolytes.

Mechanisms of chronic diarrhea

Osmotic diarrhea

- Diarrhea that stops when feeding (or medication) is discontinued is osmotic diarrhea (stops with fasting)
- Defect (Maldigestion, transport defects ingestion of unabsorbable substances).
- Stool examination (Watery, acidic, and reducing substances; increased osmolality with ion gap >100 mOsm/kg).
- No stool leukocytes.

Secretory diarrhea

- Diarrhea that persists even if the patient is fasting is secretory diarrhea
- Defect (Decreased absorption, increased secretion, electrolyte transport)
- Stool examination (Watery, normal osmolality with ion gap <100 mOsm/kg)
- No stool leukocytes

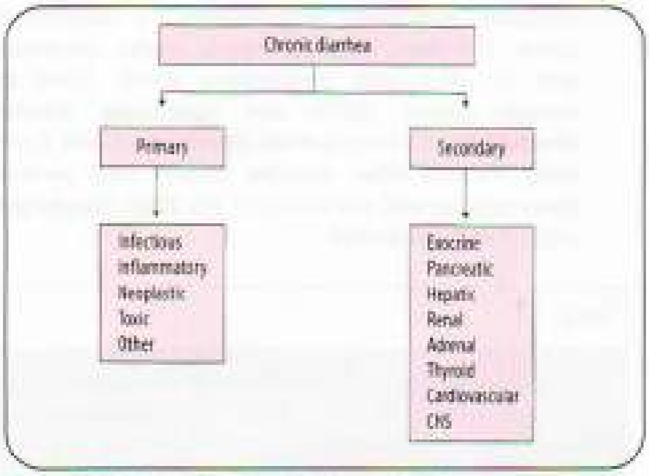


Figure 12.1: Classification of chronic diarrhea.

Main causes of chronic diarrhea

Osmotic diarrhea

- Excessive sorbitol ingestion (fruit juices)
- Enteric infections (giardia, salmonella)
- Protein energy malnutrition (maldigestion due to pancreatic insufficiency)
- Celiac disease (there is non-infectious small bowel mucosal inflammation)
- Cow's milk allergy (there is non-infectious small bowel mucosal inflammation)
- Over eating
- Antibiotics
- Post-enteritis lactase deficiency leading to lactose intolerance
- Crohn's disease, ulcerative colitis
- Cystic fibrosis (there is maldigestion due to pancreatic insufficiency)
- Chronic non-specific diarrhea (toddler's diarrhea)
- Irritable bowel syndrome
- Laxatives
- Hyperthyroidism

Secretory diarrhea

- Hirschsprung disease
- Bacterial overgrowth
- Immunoadherent Escherichia coli
- T-cell immunodeficiency
- Congenital or acquired partial small bowel obstruction

Clinical findings

- The stools may be watery, fatty, or blood may be present in the stool.
- When chronic diarrhea persists, malabsorption syndrome results. The early manifestations of malabsorption are frequent bulky oily stools (steatorrhea), weight loss and increased appetite. Late manifestations include failure to thrive, muscle wasting, protuberant abdomen, and secretory immune deficiency. These children are prone to repeated infections, which leads to further malnutrition.
- Malnutrition □Diarrhea □Malnutrition
- Nutritional disorders produced by malabsorption of specific nutrients may be present such as vitamin D (rickets), vitamin K (hemorrhage), vitamin B_{12} and folate (anemia), iron (anemia), and calcium (hypocalcemic tetany).

Osmotic diarrhea

CASE

A ***5-year-old*** is presents with ***chronic diarrhea***. For the last one year, he is stooling five times a day, passing a loose watery stool every time. Diarrhea is associated with crampy central abdominal pain, ***usually after eating***. He is ***taking excessive amounts of juices*** with his diet. Discontinuation of juices for a week results in complete improvement of his chronic diarrhea.

- Important points in history suggestive of osmotic diarrhea are:
    - Over eating
    - Excessive fluid (especially fruit juices) or excessive sorbitol intake
    - Acquired lactose intolerance
- It is confirmed by response to management rather than diagnostic tests.
- In osmotic diarrhea, the osmolality in diarrheal stool is mainly due to unabsorbed or inabsorbable osmotic load (normal stool osmolality is 280–330 mOsm/L). Active chloride secretion is the basic mechanism leading to secretory diarrhea. Active chloride secretion produces an osmotic gradient leading to movement of fluid passively from plasma into intestinal lumen.
- **Maldigestion:** Cardinal sign of maldigestion is steatorrhea. In maldigestion due to pancreatic insufficiency, there is decreased luminal hydrolysis of carbohydrates, lipids, and proteins.
- **Lactose intolerance:** Lactose deficiency results in impaired hydrolysis of lactose at the enterocyte membrane in the absence of mucosal injury. Lactase is present only in mature enterocytes at the tip of the villus. In recovery phase of viral gastroenteritis, there is an increase in enterocyte migration rate which results in less mature enterocytes in the villus tip. These less mature enterocytes have less lactase activity leading to lactose intolerance. Usual clinical manifestations of lactose intolerance are watery diarrhea, bloating, flatulence, and crampy abdominal pain. Lactose intolerance is suggested by an acid pH of stool. Reducing substance in stool is also positive.
- **Cow's milk protein allergy:** Chronic diarrhea due to cow's milk or soy protein sensitivity is also an important cause. Majority of cases begin within the first three months of life. There is gradual onset of

watery or bloody mucoid diarrhea. Associated symptoms are vomiting, anorexia, and irritability.

- **Excessive sorbitol ingestion:** Sorbitol is present in fruits and juices and is used as sweetening agent. It is poorly absorbed by the small intestine and when ingested in large amounts may produce osmotic diarrhea.
- **Enteric infections:** Enteric pathogens cause osmotic diarrhea by:
    - Invasion of the intestine (organisms that invade epithelial cells and lamina propria produce a profound local inflammatory response).
    - Enterotoxin production [Enterotoxin causes secretion of electrolytes and water by stimulating cyclic AMP (Adenosine Monophosphate) in small intestinal mucosal cells].
    - Cytotoxin production produces inflammation by causing cell injury and producing inflammatory mediators.
    - Mucosal adherence with damage to the microvillus membrane.
- Excessive intraluminal bacteria produce many enzymes and metabolic products. These destroy the glycoprotein enzymes on the brush border and disturb the monosaccharide and electrolyte transport. Due to villus injury, there are patchy, mucosal lesions leading to subtotal villus atrophy. There is marked sub-epithelial inflammatory response.
- **Extra-intestinal infections:** Infections of the urinary tract and upper respiratory tract (especially otitis media) may be associated with diarrhea. It is called parenteral diarrhea. This may be due to:
    - Antibiotic treatment of the primary infection.
    - Toxin released by infective agents.
    - Local irritation of the rectum (in UTI).
- **Malnutrition:** Malnutrition is associated with:
    - Increased frequency of enteral infections
    - Decreased bile acid synthesis
    - Decreased pancreatic enzyme output
    - Decreased disaccharide activity
    - Altered motility
    - Changes in intestinal flora
- **Antibiotics:** All classes of antibiotics may be associated with diarrhea. Diarrhea accompanies antibiotic therapy in about 60% of cases. Some antibiotics may decrease carbohydrate transport and intestinal lactase levels. Some antibiotics eradicate normal gut-flora and overgrowth of other organisms.
- **Over eating:** There is relative deficiency of pancreatic amylase in young infants and this may produce diarrhea after starchy food. Fruit juices and intestinal irritants (spices and food high in roughage) may produce diarrhea.
- **Chronic, non-specific diarrhea of infancy, toddler's diarrhea, and irritable bowel syndrome:** There is no anatomic, infectious, inflammatory, or biochemical cause. Diarrhea most commonly begins insidiously with no identifiable precipitating event. There are normal watery stools and sometimes diarrhea alternating with constipation. Diarrhea is rarely during sleep. Parents often describe formed food particles (peas and carrots) and mucus in the stool. Weight gain and growth are normal.

CASE

Toddler's diarrhea: A ***15-month-old child*** presents with a 5-month history of intermittent diarrhea. He ***posses many stools*** per day ***containing food particles. Growth*** and ***physical examination*** is ***normal***.

Secretory diarrhea

- Possibility of secretory diarrhea is present when:
    - Stool frequency is more than five times per day.
    - Diarrhea is watery and of large volume (saturating more than 75% of the diaper)
    - Diarrhea occurs throughout the day and night.
    - If secretory diarrhea is suspected, child usually requires hospitalization. Complete bowel rest is given (nothing per oral). Intravenous fluids are given to correct dehydration. If in spite of all these measures, diarrhea persists for more than 24–48 hours, it is suggestive that diarrhea is secretory.

Investigations

- **Blood examination:** ESR, hemoglobin, TLC, DLC
- **Serum electrolytes**
- **Stool** (microscopy) for ova and parasites (three fresh specimens), pus cells, or blood
- **Stool culture**
- **Stools for eosinophils**
- **Stool pH** and reducing substances
- **Hydrogen breath test.** Principle is that hydrogen gas is produced by bacterial fermentation of carbohydrates. Therefore, if lactose is inadequately absorbed by small intestine, it results in the production of hydrogen gas by colonic bacteria. Results can be false negative when the child is on antibiotics.
- **D-Xylose test:** It provides index of integrity of mucosal carbohydrates absorption. D-Xylose 14.5 g/m^2 is given orally and serum level is measured one hour after ingestion. (Normal >36 mg/dl)
- **Sudan stain** of stool for presence of fat.
- **Fecal fat:** A diet high in long chain fatty acids (2 g/kg) is given for 3 days. All stools for next 72 hours are collected. Fat malabsorption is suspected if more than 7% dietary fat is excreted in the stool.
- **Screening test for celiac disease:** Serology according to age and level of IgA.

- **Sweat chloride test** for cystic fibrosis: It is diagnostic if more than 60 mmol/L is present on two separate occasions.
- **Barium meal and barium enemas:** These are helpful for the diagnosis of inflammatory bowel disease, Hirschsprung's disease and blind loops.
- **Peroral, transpyloric jejunal biopsy:** It is indicated in celiac disease, giardiasis, and lymphangiectasia. In celiac disease, duodenal biopsy is equally diagnostic.
- **Endoscopy:** Direct visualization of mucosa of small gut, colon and hepatobiliary tract is possible and biopsy can be taken simultaneously. It is helpful in ulcerative colitis and colonic involvement of crohn's disease.

Management

- Evaluation of chronic diarrhea requires:
  - Characterization of the diarrhea
  - Establishment of an individualized differential diagnosis
  - Appropriate use of laboratory tests and in some cases, empiric management to arrive at the correct diagnosis.
- Specific etiologies of chronic diarrhea are treated accordingly as given below:
  - Infections: Bacterial infections should be treated with antibiotics. Giardia lamblia is treated with metronidazole.
  - Postinfectious diarrhea: These patients usually respond to elemental formulas such as Pregestimil, Nutramigen, which improve absorption across damaged intestinal epithelium.
  - Lactose intolerance: Once diagnosis is established, treatment is dietary exclusion of all lactose containing food. Lactose free formula can temporarily be used during acute illness.
  - Milk protein allergy: GIT symptoms resolve when offending antigen is removed.
  - Irritable bowel syndrome: Therapy consists of high fiber diet, fiber supplements and behavioral modifications.
  - Celiac disease: Gluten-free diet should be given life-long. Once diagnosis is established, avoid wheat and wheat products.
  - Cystic fibrosis: Education of patient and parents is recommended. Pancreatic enzyme replacement is given with meals. Up to 85–90% of patients require digestive therapy, which include diet adjustment, i.e. low fat, high protein and caloric diet.
  - Inflammatory bowel disease: No curative medical therapy is available. Supportive measures are important.
  - Hirschsprung enterocolitis: Acute episode is treated with antibiotics and fluid replacement. Treatment of Hirschsprung disease is surgical.

LACTOSE INTOLERANCE

CASE

A 2-year-old otherwise healthy girl presents with a complaint of intermittent ***abdominal distention***, crampy abdominal pain, and ***excessive flatulence***. She improves when only solid diet is given. Symptoms are apparent when ***she drinks excessive milk***.

- **Congenital lactase deficiency** is associated with symptoms occurring on exposure to lactose in milk.
- The brush-border lactase is expressed at low levels during fetal life. Activity increases in late fetal life and peaks from term to 3 years.
- **Secondary lactose intolerance** follows small bowel mucosal damage (celiac disease, rotavirus infection) and is usually transient, improving with mucosal healing.
- Lactase deficiency can be diagnosed by:
  - H_2-breath test.
  - Measurement of lactase activity in mucosal tissue demonstrated by small bowel biopsy.
- Diagnostic testing is not mandatory, and often simple dietary changes that reduce or eliminate lactose from the diet relieve symptoms.
- Treatmentof lactase deficiency consists of a milk-free diet.
- A lactose-free formula (based on either soy or cow's milk) can be used in infants.
- In older children, low-lactose milk can be consumed.
- Addition of lactase to dairy products may improve the symptoms.
- Yogurt contains bacteria that produce lactase enzymes and is therefore tolerated in most patients with lactase deficiency.
- Hard cheese has a small amount of lactose and is generally well tolerated.

COW MILK PROTEIN ALLERGY

CASE

A 3-month-old baby girl presents with ***chronic diarrhea***. She is taking cow's milk. Sometimes, stool is blood stained ***with mucus***. She is ***irritable*** and ***colicky***.

- Cow's milk is a common cause of food allergy (intolerance) in infants.
- Milk protein allergy is more common in males than females and in young infants with a family history of atopy.
- The estimated prevalence is 0.5–1.0%.
- Main symptoms are colic, vomiting, and diarrhea. Stools often contain small flecks of blood and mucus.
- The diagnosis is usually made clinically.

- Treatment of cow's milk allergy involves elimination of cow's milk and its products from the diet and substitution with an appropriate formula in babies.
- However, avoiding dairy products in children is not easy. It is therefore important to avoid any food which contains cow's milk, cheese, butter, ghee, butter milk cream, milk powder, whey, casein, and margarines which contain milk products.
- If long term exclusion is required, patients require an alternative source of calcium and protein. This applies to the affected child and to mother if dietary exclusion during breastfeeding is required.
- After confirming cow's milk allergy, replacing dairy products with alternative formulae, may include:
  - **Soy protein formula**: About 50 to 80% of children with cow's milk allergy can tolerate soy based formulae. However, in children allergic to soy as well, it is not a suitable substitute.
  - **Extensively Hydrolyzed Formula (EHF):** This is cow's milk based formula that has been treated with enzymes to break down most of the proteins that cause symptoms in infants who are allergic to cow's milk.
  - **Amino acid based formula:** This formula is necessary in around 10 per cent of children with cow's milk allergy. This formula is tolerated by almost all children with soy or cow's milk allergies.

CONSTIPATION

CASE

Chronic functional constipation: A 2-year-old healthy boy presents with a history of ***difficulty passing stools*** from 8 months. Stooling was ***normal since birth*** until solids were introduced at 6 months (so hirschusprung disease is ruled out). There are streaks of blood on the surface of the stools.

- Constipation is passage of bulky or hard stool with difficulty at infrequent intervals.
- Retention of feces in the rectum results in encopresis (involuntary fecal leakage) in about 60% of constipated children.
- Most common cause of constipation in childhood is voluntary or involuntary retentive behavior.
- Pathophysiology :

  Two fundamental factors contributing to constipation are:

  1) Defects in emptying the rectum leading to stool retention (lesion of the rectal muscles, Pelvic floor, abdominal muscles, disorders of anal sphincter relaxation fall into this group)
  2) Defects in filling the rectum, it may be encountered whenever there is poor gut peristalsis (Hypothyroidism, loperamide, opiates) or in case of mechanical structural lesion (Hirschsprung's disease)

Table 12.3: Findings consistent with functional constipation

History
Stool passed within 48 hours of birth Extremely hard stools, large-caliber stools Fecal soiling (encopresis) Pain or discomfort with stool passage Withholding of stool Blood on stools Perianal fissures Diet low in fiber or fluids, high in dairy products Avoiding the toilet
Physical examination
Mild abdominal distention Palpable stool in left lower quadrant Normal placement of anus Normal anal sphincter tone Rectum packed with stool Rectum distended Presence of anal wink and cremasteric reflex

- Retentive constipation should be distinguished from Hirschsprung's disease.
- Findings consistent with **Hirschsprung's disease**:
  - Age of onset is at birth.
  - There is abdominal distention.
  - Nutrition and growth will be poor.
  - Soiling and retentive behavior is rare.
  - On rectal examination, ampulla may be empty.
  - On rectal biopsy ganglion cells are absent.
  - On rectal manometry, there is non-relaxation of internal anal sphincter after rectal distention.
  - On barium enema, there is narrow distal segment with proximal megacolon.

Management

- Increased intake of fluids and high-residue food such as bran, whole wheat, fruits, and vegetables are given.
- In severe cases, stool softeners are used to prevent excessive drying of the stool.
- The prevention of stool holding and the establishment of a regular bowel habit are accomplished by toileting the child at regular times each day and by the daily administration of stool softeners over several months.
- Psychiatric consultation may be needed in patients with resistant symptoms or severe emotional disturbances.

APPROACH TO ABDOMINAL PAIN

CASE

Functional abdominal pain: A seven-year-old child presents with a history of ***intermittent abdominal pain*** for the last 3 months. The pain is generalized and is not associated with any change in bowel habits. Symptoms ***increase during school time***. ***Abdominal examination*** is ***unremarkable***. ***Laboratory investigations*** are ***normal***.

- Abdomen-related complaints make up 9–10% of all pediatric emergencies. This does not include extraabdominal conditions, which may also present as abdominal pain.
- Abdominal pain may arise from one of the three sources:
  - Intraabdominal disease
  - Extraabdominal disease
  - Systemic disease
- The three intraabdominal sources are:
  - Distention of a hollow viscus
  - Peritoneal inflammation
  - Organ ischemia

Chronic abdominal pain

- Long-lasting intermittent or constant abdominal pain that is functional or organic (disease based).

Functional abdominal pain

- Abdominal pain without demonstrable evidence of pathologic condition, such as anatomic metabolic, infectious, inflammatory or neoplastic disorder.

Functional dyspepsia

- Functional abdominal pain or discomfort in the upper abdomen is called functional dyspepsia.

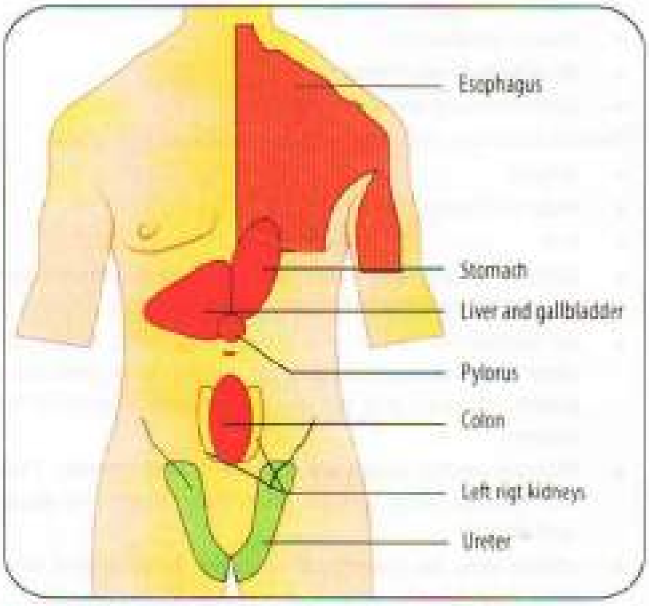


Figure 12.2: Main sites of referred abdominal pain.

Irritable bowel syndrome

- This is functional abdominal pain associated with alteration in bowel movements.

Abdominal migraine

- This is functional abdominal pain with features of migraine (paroxysmal abdominal pain associated with anorexia, nausea, vomiting or pallor as well as maternal history of migraine headaches).

Functional abdominal pain syndrome

- Functional abdominal pain which interferes with daily functioning or is accompanied by somatic symptoms including headaches, limb pain or difficulty in sleeping is labelled as Functional Abdominal Pain syndrome

Main causes of acute pain abdomen

Gastrointestinal tract disorders

- Appendicitis
- Peptic ulcer disease
- Gastritis
- Pancreatitis
- Gasteroenteritis
- Hepatitis
- Constipation
- Food poisoning
- Abdominal trauma
- Cholecystitis

Genitourinary disorders

- Urinary tract infection
- Renal calculus
- Testicular torsion
- Orchitis/epididymitis
- Pelvic inflammatory disease.

Systemic disorders

- Diabetic ketoacidosis
- Hemolytic uremic syndrome
- Porphyria
- Sickle cell disease

Miscellaneous

- Colic
- Pneumonia
- Tumors

Symptoms and signs of abdominal pain needing investigations

- Pain that wakes up the child from sleep
- Persistent right upper or right lower quadrant pain.
- Significant vomiting (bilious or protracted vomiting)
- Unexplained fever
- Genitourinary tract symptoms
- Dysphagia
- Chronic severe diarrhea or nocturnal diarrhea
- Gastrointestinal blood loss

- Involuntary weight loss
- Deceleration of linear growth
- Family history of inflammatory bowel disease, celiac disease, and peptic ulcer disease
- Localized tenderness in the right upper quadrant
- Localized tenderness in the right lower quadrant
- Localized fullness or mass
- Hepatomegaly
- Splenomegaly
- Jaundice
- Perianal disease
- Abnormal or unexplained physical findings
- Hematochezia
- Anemia

Diagnosis

- **Radiology**
    - Plain radiographs may be diagnostic in certain conditions, such as fecalith in a child with lower quadrant pain (appendicitis), a ruptured viscus, a bowel obstruction, or pneumonia. Plain radiographs may suggest other conditions such as a mass, intussusception, or medial displacement of the stomach bubble from a splenic hematoma.
    - In addition to plain radiographs, other imaging procedures such as barium enema, CT scan, and USG abdomen are considered as directed by the history and physical examination.
- **Laboratory tests**
    - **CBC+ ESR**
    - **CRP**
    - **Metabolic profile**
    - **Serum Amylase, Lipase**
    - **Urinalysis**
    - **Fecal Calprotectin (Screening test for IBD)**
- **Endoscopy** (Optional)

Management

- Management of the child often precedes the establishment of the diagnosis.
- If the child is hemodynamically unstable because of fluid losses, immediate intravenous access and fluid resuscitation are given.
- Further stabilization may require gastric decompression with nasogastric tube aspiration and Foley catheter insertion for monitoring urine output and collecting specimens.
- Appropriate antibiotic coverage or initial treatment of ingested toxins should also be considered.
- Early medical or surgical consultation is mandatory for coordinated evaluation and management.
- Treatment of functional abdominal pain is reassurance and education of the child and family. The child and family should be reassured that no evidence of a serious underlying disorder is present.
- For chronic abdominal pain with irritable bowel syndrome and non-stimulating laxatives are used.

PEPTIC ULCER DISEASE

CASE

A 10-year-old boy presents with ***recurrent pain epigastrium*** for about 3 months. Pain awakens him from sleep. Eating food sometimes helps to relieve pain. Occasionally, he vomits after the onset of pain and sometimes there is ***frank blood in vomiting***. Occult blood has been found in his stool.

- Peptic ulcers may occur at any age but are more common between 12–18 years. Boys are affected more frequently than girls.

Classification

- Primary (peptic) ulcers are usually chronic and duodenal.
- Secondary ulcers are caused by factors that affect integrity of gastric mucosa. They are Usually acute and gastric in nature.

Pathology

Many factors are important in the development of peptic ulcer disease:

- Gastric acidity
- Blood group O
- High serum levels of pepsinogen I
- Positive family history (in 25–50% children with duodenal ulcer)
- Emotional strain
- Gastric acidity may be low or normal in case of gastric ulcers and increased in case of duodenal ulcers

Gastric tissue resistance is maintained by:

- Cell turnover
- Mucus production
- Bicarbonate secretion
- Local prostaglandin synthesis

Factors lowering resistance to acid-induced injury are:

- Anoxia
- Poor perfusion
- Bile
- Drugs (especially nonsteroidal anti-inflammatory agents that inhibit prostaglandin synthesis).
- An important factor in childhood gastritis and peptic ulcer disease is *Helicobacter pylori*. It is present in gastric mucosa and is common in low socioeconomic classes.
- Primary peptic ulcers are duodenal and chronic. These are related to *H. pylori*. Secondary ulcers are gastric and acute.
- Ulcers may be superficial or deep. Deep ulcers erode into the mucosa and submucosa. If it penetrates a

blood vessel, hemorrhage may occur. Deep ulcers may cause perforation.

- Most gastric ulcers are present on the lesser curve or antral area. Most duodenal ulcers are on the posterior wall and duodenal bulb.
- In ulcer, a fibrinous coat of leukocytes and red cells covers a zone of fibrinoid necrosis surrounded by an infiltration of acute and chronic inflammatory cells.

Primary (peptic) ulcers

Clinical findings

- There is vomiting, acute and chronic gastrointestinal bleeding, and pain abdomen.
- Gastrointestinal blood loss may be in the form of hematemesis, hematochezia, or melena. This leads to iron deficiency anemia.
- Pain is usually in epigastrium. It is dull or aching in character. Pain may last from minutes to hours. Exacerbations and remissions may last from weeks to months.
- With duodenal ulcers, pain typically occurs several hours after meals and often awakens the patient at night. Nocturnal pain is common in duodenal ulcers and eating tends to relieve the pain.
- Gastric ulcers differ in that pain is commonly aggravated by eating, resulting in weight loss.
- In about 33% of cases, there may be relief of pain after taking antacids.
- If in rare cases, ulcer penetrates into the abdominal cavity, there is shock, anemia, peritonitis, or pancreatitis.

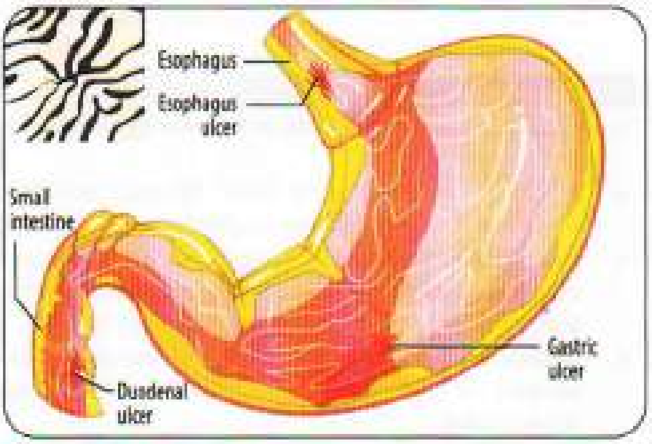


Figure 12.3: Peptic ulcer disease.

Diagnosis

- X-ray abdomen after barium meal:
  - It may show ulcer crater.
- Endoscopy:
  - It is the investigation of choice.
- If the purpose of endoscopy is to identify the site of acute upper GIT bleeding, it should be performed within 48 hours after the episode.
- Endoscopy allows the direct visualization of esophagus, stomach, and duodenum, identifying the specific lesions.
- Biopsy specimens can be obtained from the esophagus, stomach, and duodenum for histologic assessment as well as for *H. pylori* infection screening.
- Endoscopy also provides the opportunity for hemostatic therapy including injection and electrocoagulation if necessary.
- Fecal enzyme immunoassay tests for *H. pylori* are also available.
- Serologic assays using validated immunoglobulin G antibody detection may be helpful for screening children for the presence of *H. pylori*.
- 13C-urea breath tests and stool antigen tests are also non-invasive methods of detecting *H. pylori* infection.

Differential diagnosis

- Esophagitis
- Giardiasis
- Pancreatitis
- Inflammatory bowel disease
- Cholelithiasis
- Recurrent abdominal pain of childhood
- Functional, nonspecific pain (it is not associated with weight loss, emesis, blood loss, and preprandial or night pain)

Management

- Main aims of treatment are:
  - To hasten healing of the ulcer
  - To relieve pain
  - To eliminate the primary cause
  - To prevent complications
- Anemia and hemorrhagic shock are treated if present. The management of acute hemorrhage includes serial monitoring of pulse, blood pressure, and hematocrit to maintain hemodynamic stability. Normal saline can be used to resuscitate a patient who has poor intravascular volume status. This can be followed by packed red blood cell transfusions for symptomatic anemia.
- Food that cause pain should be avoided. Caffeine should be avoided as it increases gastric secretion. Aspirin and other nonsteroidal anti-inflammatory drugs should not be used.
- Gastric acidity should be suppressed. Antacids are given 1–3 hours after a meal and at bedtime. Dose as much as 1 ml/kg/dose has been recommended.
- H_2 receptor blockers are also effective. Cimitidine (20–40 mg/kg/day in four divided doses) is commonly used. It is given orally before meals and at bedtime. It produces healing in 4–8 weeks.
- Proton pump inhibitor (omeprazol) also suppresses the acid production. Dose is 1 mg/kg/day in two divided doses.

- Therapy for H. pylori is given including amoxicillin (or clarithromycin), metronidazole for 2 weeks, and omeprazol for one month.
    - Amoxicillin 50 mg/kg/day in 2 divided doses
    - Clarithromycin 15 mg/kg/day in 2 divided doses
    - Metronidazole 20 mg/kg/day in 2 divided doses
    - Proton pump inhibitor (omeprazole) 1 mg/kg/day in 2 divided doses
- Surgery is rarely indicated in a case with intractable pain or chronic bleeding.

Secondary ulcers

- In secondary ulcers:
    - Normal mucosal protective mechanisms are depressed.
    - Disease causes a marked increase in gastric acid or proteolytic enzymes.
- Secondary ulcers are commonly gastric and are twice as common as primary ulcers.
- Common causes are stress and drugs.

Stress ulcers

- Common causes are:
    - Sepsis
    - Respiratory or cardiac insufficiency
    - Dehydration
    - Trauma or other life-threatening conditions (Cushing ulcers due to gastric hypersecretion).
    - Burns (Curling ulcers)
- Stress ulcers are usually multiple with hemorrhagic gastritis and erosions.
- Perforation or massive hemorrhage may occur.

Drug-induced ulcers

- Aspirin and other nonsteroidal anti-inflammatory drugs as well as corticosteroids may cause drug-related ulcers by inhibiting prostaglandin synthesis.

Management

- It is same as primary ulcers.

CELIAC DISEASE

CASE

A 2-year-old child presents with complains of increasing lethargy, diffuse crampy ***abdominal pain***, and ***loose stools*** for six months. He is ***failure to thrive***. On examination he is a ***pale*** boy with mild ***abdominal distension***. ***Weight and height*** are below the normal for his age (***below the 3rd centile***). Laboratory investigations show iron-deficiency anemia with a ***positive celiac antibody screen***.

- Celiac disease (gluten–sensitive enteropathy) is an important cause of chronic diarrhea in children.
- Celiac disease results from intestinal sensitivity (an injury to the mucosa of the small intestine) to the gliadin fraction (a protein component) of gluten from wheat, rye, and barley.
- Rice does not contain gluten and can be eaten freely.

Inheritance

- The inheritance is mainly polygenic (wheat, genetic predisposition and environmental factors).

Incidence

- Incidence is 1: 3000 births.
- Up to 2–5% of first-degree relatives have symptomatic and 10% have asymptomatic damage to small intestinal mucosa.
- There is increased incidence of celiac disease in children with type I diabetes mellitus, IgA deficiency, and Down syndrome.
- Individuals with certain HLA types (DR3, DR4, DQW2, and B8) are at higher risk.

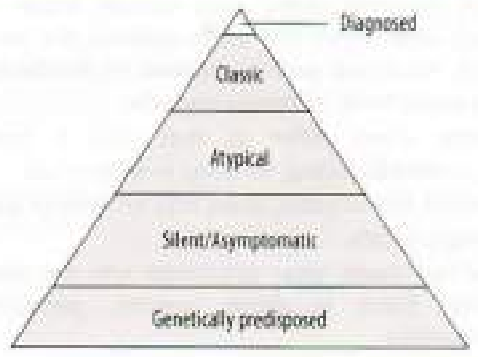


Figure 12.4: The celiac iceberg.

Pathogenesis

- Gliadin (a fraction of gluten in the wheat) damages the small intestine.
- Intestinal damage results from humoral and T-cell mediated immune response to gliadin.
- Raised levels of IgA as a result of mucosal stimulation may occur and IgA-associated anti-gliadin, reticulin, and endomysium antibodies are frequently present.
- Surface epithelial cells are destroyed, the villi become blunted or flat (villous atrophy), and the crypts hypertrophy.
- There is lymphocytic and plasma cell infiltration.
- Brush border enzyme levels are greatly decreased.

Clinical findings

- Clinical features of celiac disease vary considerably.
- Most children show symptoms between 6 and 24 months of age after starting the wheat products in weaning. Symptoms can begin at any age when gluten-containing food are given.
- Celiac disease should be suspected in any child with chronic diarrhea, vomiting, and abdominal distension.

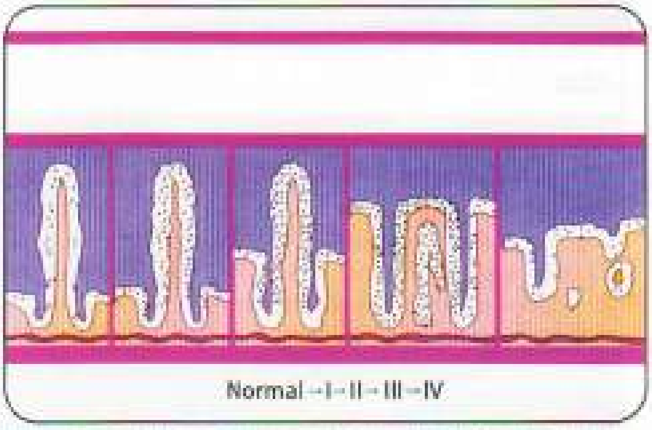


Figure 12.5: Different stages of damage to intestinal villi.

- Gastrointestinal symptoms are due to atrophy of the small bowel mucosa and malabsorption:
    - Diarrhea
    - Distended abdomen
    - Vomiting
    - Anorexia
    - Weight loss (failure to thrive)
    - Rectal prolapse
    - Aphthous stomatitis
    - Intussusception
- Hematologic symptoms are due to iron malabsorption:
    - Anemia
- Skeletal symptoms are due to calcium and vitamin D malabsorption.
    - Rickets
    - Osteoporosis
    - Enamel hypoplasia of the teeth
- Muscular symptoms are due to malnutrition:
    - Muscular atrophy
- Neurologic symptoms are due to thiamine or vitamin B_{12} deficiency:
    - Peripheral neuropathy
    - Epilepsy
    - Irritability
    - Cerebral calcifications
    - Cerebellar ataxia
- Endocrinologic symptoms are due to malnutrition and calcium and vitamin D malabsorption:
    - Short stature
    - Delayed puberty
    - Secondary hyperparathyroidism
- Dermatologic symptoms are due to autoimmunity:
    - Dermatitis herpetiformis
    - Alopecia areata
    - Erythema nodosum
- Respiratory symptoms:
    - Idiopathic pulmonary hemosiderosis
- **Silent celiac disease:** Seen in asymptomatic 1st degree relatives who show severe mucosal damage on biopsy.
- **Potential celiac disease:** In which TG2 antibodies can be detected in situ without any histologic abnormalities.
- **Latent celiac disease:** In which subjects show normal histology but show gluten enteropathy at time.

Diagnosis

- The diagnosis of celiac disease is based on a combination of:
    - Symptoms
    - Antibodies
    - HLA
    - Duodenal histology
- Antitransglutaminase IgA antibody and anti-endomysial IgA antibody are diagnostic.
- Because IgA deficiency is common in celiac disease, total serum IgA also must be measured to document the accuracy of these tests.
- In the presence of IgA deficiency, this test may be falsely negative.
- In the absence of IgA deficiency, either test yields a sensitivity and specificity of 95%.
- Antigliadin antibodies are not reliable for screening.
- If antibody is positive, an endoscopic jejunal biopsy is performed. Demonstration of partial or subtotal villous atrophy and crypt hyperplasia is consistent with the diagnosis.
- Intestinal biopsy is the most reliable test for celiac disease.
- Other laboratory findings are excessive fecal fat, impaired carbohydrate absorption, hypoproteinemia and anemia.

Differential diagnosis

- Other causes of malabsorption.
    - Autoimmune enteropathy
    - Tropical sprue
    - Giardiasis

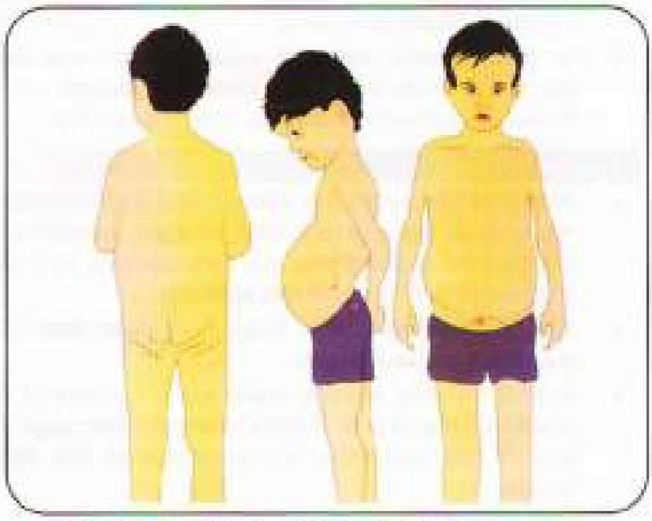


Figure 12.6: Clinical features of celiac disease.

- Bacterial overgrowth
- Crohn disease
- Eosinophilic gastroenteritis
- Cow's milk enteropathy
- Soy protein enteropathy
- Primary immunodeficiency
- Protein energy malnutrition
- Nongluten food intolerances

Management

- **Treatment of celiac disease is the provision of a gluten-free diet for life.**
- Gluten free is defined as <20ppm, and gluten threshold to be set to <50 mg/day.
- This requires a wheat-, barley-, and rye-free diet.
- Clinical improvement is usually evident within a week and histologic repair is complete after 3–12 months. Anti-gliadin antibody levels should fall with a gluten-free diet, and rise on rechallenge.
- Restriction of lactose and iron supplementation may be necessary for several weeks to months as the small intestinal mucosa heals. Normal amounts of fat, rice or corn flour bread, fruits, proteins, milk, eggs, and vegetables are advisable. Supplemental calories, vitamins, and minerals are indicated in acute phase.
- Corticosteroids are indicated only in very ill patients with signs and symptoms of celiac crisis (profound malnutrition, diarrhea, edema, abdominal distention, and hypokalemia). They can hasten the clinical improvement.

Silent celiac disease

- Silent celiac disease (without any apparent signs and symptoms) may be present in children with nonspecific GI complaints, growth failure, type 1 diabetes, thyroid disease, vitiligo, IgA deficiency, and Down syndrome, and in family members of celiac patients.
- Treatment is recommended with gluten-free diet for a symptom-free child with positive serology and positive intestinal biopsy specimens.
- In children with potential celiac disease who have positive serology but normal intestinal biopsies, careful follow-up without diet therapy is recommended.

Prognosis

- After starting gluten-free diet, clinical and histological recovery is the rule but may be slow. Lessening of diarrhea follows and later diarrhea subsides. First sign is improvement of mood and appetite.
- No complications from long-term gluten-free diet treatment are recognized.
- In long standing disease, malignant lymphoma of the small intestine occurs. Dietary treatment decreases the risk of this and other complications of the celiac disease.

INFLAMMATORY BOWEL DISEASE (IBD)

CASE

A 13-year-old girl presents with a ***seven month history of diarrhea***, with central crampy ***abdominal pain***, lethargy, and ***weight loss***. She is anemic. On investigations, she has ***raised Erythrocyte Sedimentation Rate*** (ESR) and C-Reactive Protein (CRP) and low albumin. Stool examination shows no bacterial growth, no ova, cysts or parasites. Small bowel followed through, upper endoscopy and ***colonoscopy*** confirms the diagnosis.

- Crohn's disease and ulcerative colitis are the two major idiopathic inflammatory bowel diseases of children.
- There are many features common in both Crohn's disease and ulcerative colitis. These include diarrhea, pain abdomen, fever, and blood loss.
- Cause of IBD is unknown but an abnormal or uncontrolled, genetically determined immunologic or inflammatory response to an environmental antigenic trigger, possibly a virus or bacteria may be responsible.
- Crohn's disease may involve any part of the GIT (mouth to anus), whereas ulcerative colitis produces only colonic disease.
- Peak incidence of IBD in children is in the second decade of life.

Table 12.4: Comparison of Crohn's disease and ulcerative colitis.

Feature	Crohn's disease	Ulcerative colitis
Malaise, fever, weight loss	Common	Common
Rectal bleeding	Sometimes	Common
Abdominal mass	Common	Not present
Abdominal pain	Common	Common
Peri-anal disease	Common	Rare
Ileal involvement	Common	None (backwash ileitis)
Rectal involvement	Occasional	Universal
Strictures	Common	Unusual
Fistula	Common	Very rare
Skip lesions	Common	Not present
Transmural involvement	Usual	Not present

Crypt abscesses	Variable	Unusual
Intestinal granuloma	Common	Rarely present
Risk of cancer	Increased	Greatly increased
Erythema nodosum	Common	Less common
Mouth ulceration	Common	Rare
Auto-immune hepatitis	Rare	Common
Sclerosing cholangitis	Rare	Common
Perinuclear antineutrophil cytoplasmic antibody–positive	<20%	70%

Clinical findings

Ulcerative colitis

- Children present with:
    - Blood in stool (100%)
    - Abdominal pain (95%)
    - Tenesmus (75%)
- Mild disease is present in 90% of patients. It is characterized by:
    - Less than 4 stools per day
    - No fever
    - Anemia
    - Hypoalbuminemia
- Moderate disease is characterized by:
    - More than 6 stools per day
    - Fever
    - Anemia
    - Hypoalbuminemia
- Severe disease is characterized by:
    - High-grade fever
    - Abdominal tenderness
    - Distention
    - Tachycardia
    - Leukocytosis
    - Hemorrhage
    - More than 10 stools per day
    - Severe anemia
- Toxic megacolon: It is a life threatening complication of ulcerative colitis, characterized by:
    - Fever
    - Abdominal distension and pain
    - Massively dilated colon
    - Anemia
    - Low serum albumin due to fecal protein losses.

Crohn's disease

- It is often subtle with:
    - Crampy abdominal pain
    - Fever of unknown origin
    - Weight loss
    - Bloody diarrhea
    - Arthritis preceding GIT manifestations

Extra-intestinal manifestations

(Much more common in Crohn's disease)

- Fever
- Stomatitis (apthous ulcers)
- Weight loss
- Delayed growth and sexual development
- Arthralgias
- Polyarticular arthritis
- Primary sclerosing cholangitis (mainly in ulcerative colitis)
- Chronic active hepatitis
- Sacroiliitis
- Pyoderma gangrenosum
- Erythema nodosum
- Nephrolithiasis
- Uveitis or episcleritis
- Gall stones

Diagnosis

- Careful history and examination is needed.
- On X-ray with a double (air)–contrast barium enema demonstrates:
    - Diffuse colonic lesions and pseudopolyp formation in ulcerative colitis
    - Focal ileal and/or colonic involvement with skipped lesions, rectal sparing, segmental narrowing (string sign), and longitudinal ulcers in Crohn's disease
- Endoscopy is also helpful to visualize mucosa and to take biopsy.

Differential diagnosis

- Chronic bacterial or parasitic causes of diarrhea such as Clostridium difficile, Campylobacter jejuni, Yersinia enterocolitis, amebiasis, and giardiasis
- Systemic lupus erythematosis
- Rheumatoid arthritis

Management

Medical treatment

- A medical cure for ulcerative colitis is not available.
- Treatment is aimed at controlling symptoms and reducing the risk of recurrence.
- **Diet:**

- High-protein, high-carbohydrate diet with normal amounts of fat is given. There should be adequate caloric intake.
- Decreased amounts of roughage are given.
- Lactose is not given due to poor tolerance in active disease.
- Vitamins, iron, and zinc are also given.

- **Non-absorbable salicylate derivatives:**
  - Salfasalazine: It is effective in mild cases. It is not absorbed in small intestine and hydrolyzed by colonic flora into sulfapyridine and 5-aminosalicylate. It has local anti-inflammatory action in the colon.
  - The dose of sulfasalazine is 50–75 mg/kg/24 hours (divided into 2–4 doses). Maximum dose is 2–4 g/24 hours.
- **Probiotics:**
  - Probiotics are effective for maintenance of remission for ulcerative colitis. They do not induce remission during an active flare.
- **Corticosteroids:**
  - These are used in more severe inflammatory bowel disease.
  - Prednisone: usual starting dose of prednisone is 1–2 mg/kg/24 hours (40–60 mg maximum dose). This medication can be given once daily.
- **Azathioprine:**
  - Many children with disease requiring frequent corticosteroid therapy are started on immunomodulators such as azathioprine (2.0–2.5 mg/kg/day) or 6-mercaptopurine (1–1.5 mg/kg/day).
- **Metronidazole:**
  - It is used in Crohn's disease with peri-anal involvement.
  - It is also effective in Crohn's disease of the colon.
  - Dose is 15–30 mg/kg/day in three divided doses.
  - Ciprofloxacin have similar therapeutic effects.
- **Cyclosporin.**
  - It is a powerful immunosuppressant and is effective in severe, steroid-resistant ulcerative colitis.
  - Side effects and rapid relapse after discontinuation are common.
  - It is used in severely affected patients for whom surgical treatment is planned.
- **Anticytokines** (Infliximab)

Surgical treatment

- Crohn's disease is not cured by surgery.
- Surgery is curative in ulcerative colitis. Colectomy is performed for intractable disease, complications of therapy, and fulminant disease that is unresponsive to medical management.
- About 70% of patients with Crohn's disease require surgery to relieve intractable symptoms, or encourage growth and sexual maturation.
- In ulcerative colitis, surgery is indicated in uncontrolled hemorrhage, toxic mega colon, unrelenting pain and diarrhea, growth failure, high-grade mucosal dysplasia, or malignant tumors.

Prognosis

- In Crohn's disease mortality is low (2% in first 7 years) but morbidity is high. About 20% have mild disease and about 20% have severe disease.
- Prognosis is good in ulcerative colitis. About 5% patients present with toxic megacolon requiring immediate colectomy. About 20–40% patients require colectomy due to pancolitis, anemia, and hypoalbuminemia.

HEPATOMEGALY

CASE

A 5-year-child presents with fever and jaundice. On examination, she has enlargement of liver (hepatomegaly) 3 cm below costal margin.

Causes of hepatomegaly

Neonates

- Congenital infections (CMV, Rubella, Toxoplasmosis)

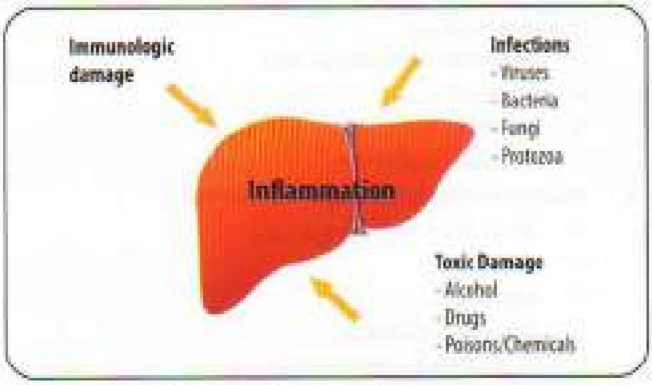


Figure 12.7: Liver is vulnerable to many damages.

Infancy and early childhood

- Hepatitis
- Congestive cardiac failure
- EBV
- Mucopolysaccharidosis
- Leukemia
- Lymphoma
- Septicemia
- Thalassemia
- Reye syndrome
- Osteopetrosis
- Metabolic disorders:
  - Wilson's disease

  - Cystic fibrosis
  - Hemochromatosis
  - Glycogen storage disease
  - Lipid storage disease

ACUTE HEPATITIS

- Acute hepatitis is characterized by inflammation and necrosis of the liver.
- The underlying trigger for the inflammatory process may be:
- Toxic causes
  - Autoimmune causes
  - Infective causes
  - Metabolic causes
- Acute infective disorders of the liver may be:
  - Viral hepatitis
  - Bacterial, protozoal and helminth infection
  - Hepatic abscess (amebic, pyogenic)

ACUTE VIRAL HEPATITIS

- The hepatotropic viruses infect only hepatocytes. Viruses, which are not predominantly hepatotropic, may lead to hepatic inflammation as part of a more widespread disease process.

Table 12.5: Hepatotropic viruses

Virus	*Route of spread*	*Diagnostic test*	*Carrier state*	*Incubation period*
HAV	Feco oral	Anti-HAV IgM	No	15–19 days
HBV	Parenteral	HBsAg, anti-HBc IgM	Yes	60–180 days
HCV	Parenteral	Anti-HCV, PCR-RNA test	Yes	14–160 days
HDV	Parenteral	Anti-HDV	Yes	20–42 days
HEV	Feco oral	Anti-HEV	No	21–63 days
HFV	-	-	-	-
HGV	Parenteral	-	-	-

HEPATITIS A

CASE

A previously well 8-year-old boy presents with 3 days history of nausea, anorexia, ***fever***, ***yellowness of eyes***, diarrhea and ***abdominal pain***. He is passing dark urine. On examination he is febrile to 101°F, has scleral icterus, and moderate ***right upper quadrant tenderness***. Liver is moderately enlarged. ***Transaminases*** are ***raised***.

- Hepatitis A Virus (HAV) most commonly gives rise to an asymptomatic infection, with less than 5% of infected people having an identifiable illness.
- As a whole, HAV alone accounts for 20–25% of clinically apparent hepatitis.
- Major route of transmission of the HAV is feco oral; parenteral transmission has been also documented.
- In HAV endemic areas, infection in childhood is common but asymptomatic.
- With increasing age, infection is usually symptomatic.
- Mortality is increased if the age of the patient is less than 5 years.

Risk factors

- Following are the main risk factors for HAV infection:
  - Travel to the endemic area
  - Household contact with HAV infection
  - Child of age 3–10 years in household
- Fecal shedding of HAV is typically stopped by the time jaundice is apparent.
- Persons infected with HAV are contagious for about 7 days after the onset of jaundice.

Clinical findings

- HAV infection has an incubation period of 15–19 days with a mean of 30 days, replicating within the hepatocytes and leading to viremia and excretion into bile with fecal shedding.
- Symptoms are usually apparent within 28 days of exposure. A prodromal illness is characterized by anorexia, nausea, malaise and fever.
- Within a few days to a week, jaundice, pale stools and dark urine become apparent. There may be tender hepatic enlargement, splenomegaly and posterior cervical lymphadenopathy.
- Majority of the symptomatic children have an uncomplicated course with complete resolution of infection. Rarely, HAV infection may lead to fulminant hepatic failure or prolonged cholestasis.

Diagnosis

- Serologic diagnosis is made by detection of specific circulating antibody.
- Anti-HAV IgM is indicative of recent infection. Peak levels occur during the acute illness or early convalescent phase, and it persists for 4–6 months after infection.
- Anti-HAV IgG appears early, peaks during the convalescent phase and persists lifelong conferring protection.
- Aminotransferases and conjugated and un-conjugated bilirubin levels are elevated.
- Hypoalbuminemia, hypoglycemia, and marked prolongation of prothrombin time are serious prognostic findings.

Diagnostic blood tests: serology and viral PCR

Acute/active infection

- Anti-HAV IgM–positive

Past infection (resolved)

- Anti-HAV IgG–positive

Vaccine response

- Anti-HAV IgG–positive

Complications

(Extrahepatic manifestations)

- Guillain-Barre syndrome
- Postviral encephalitis
- Acute interstitial nephritis
- Autoimmune hemolytic anemia

Differential diagnosis

- Viral enteritis
- Pancreatitis
- Infectious mononucleosis
- Leptospirosis
- Drug-induced hepatitis
- Wilson's disease
- Autoimmune hepatitis
- Other hepatitis viruses
- Acquired CMV

Management

- HAV has a good prognosis with full recovery and persistence of protective antibody in the majority of the cases.
- There is no specific treatment for hepatitis A.
- During acute infection treatment is supportive.
- Supportive treatment consists of intravenous hydration.
- In those with prolonged cholestasis, fat-soluble vitamin supplementation and symptomatic relief of pruritis should be provided.
- In those patients with fulminant hepatic failure, liver transplantation should be considered.
- Drugs and elective surgery should be avoided.

Prevention

- Improving sanitation and providing education to improve standards of basic hygiene.
- Patients infected with HAV are contagious approximately
- 7 days after the onset of jaundice.
- Vaccine against hepatitis A virus is approved for children older than 2 years of age. It is administered through intramuscular route in a two-dose schedule, with the second dose given 6–12 months after the first dose. First dose provide 90% and second dose provide 100% sero-conversion.
- Human normal immunoglobulins, (0.02–0.04 ml/kg) given by intramuscular injection gives up to 3–6 months of protection against HAV. It is effective if given within 1–2 weeks of exposure.

Prognosis

- 95% of children recover without any sequelae.
- Rarely, patient develops fulminant hepatitis and patient may die in 5 days or may survive as long as 1–2 months.
- Prognosis is poor in case of hepatic coma, deepening jaundice, or development of ascites.

HEPATITIS B

CASE

A 3-year-old ***unvaccinated*** child presents for evaluation. His mother is suffering from hepatitis B. His clinical examination shows no abnormal finding. His laboratory investigations show serum bilirubin 1 mg%, ALT 25 iu/L, ***HBsAg positive***, HBeAg negative, and HB DNA negative.

- HBV may cause fulminant hepatic failure or lead insidiously to cirrhosis, with an increased risk of hepatocellular carcinoma.
- Chronic HBV carriers comprise 5% of the world population; of these 25% will develop serious liver disease.
- The likelihood to become chronic carrier is highest in infancy.

Serological markers

- Examination of the serological markers of HBV infection and their change with time allows the distinction to be made between acute hepatitis, resolved past infection, and persistent infection.
- The first serum marker to appear during acute infection is (surface antigen) sAg, occurring several weeks to months after initial exposure. It eventually disappears with clinical recovery. The eAg is also normally present during the acute phase and is indicative of a highly infectious state, with HBV DNA is also detectable in blood.
- The host response is first apparent with the appearance of IgM and IgG antibody to cAg (cAb), followed by the appearance of anti-e antibody (eAb). The IgM component eventually declines and becomes undetectable, whereas IgG persists for years.

Serological markers of HBV infection

Acute/active infection

- Anti-HBc IgM–positive
- HBsAg–positive
- Anti-HBs–negative
- HBV DNA–positive (PCR)

Past infection (resolved)

- Anti-HBs–positive
- Anti-HBc IgG–positive

Chronic infection

- Anti-HBc IgG–positive
- HBsAg–positive
- Anti-HBs–negative
- PCR–positive or negative

Vaccine response

- Anti-HBs–positive
- Anti-HBc–negative

HBV transmission

- HBV is present in infected individuals in high concentrations in blood, serum and serous exudates, semen, vaginal fluid and saliva.
- Although also found in low concentrations in feces and breast milk, these have not been associated with a significant risk of transmission.
- Parenteral and sexual exposure are the main routes of transmission.
- Children at high risk include those requiring frequent transfusions e.g. with hemolytic anemia, thalassemia, or hemophilia.
- Household transmission of HBV from infected family members may occur.
- Up to 40% of children who are born to carrier mothers but not infected at birth acquire infection in the first 5 years of life.

Perinatal transmission

- Exposure to maternal blood transmits HBV.
- The most important risk factor for acquiring of HBV is perinatal exposure to an HBsAg-positive mother.
- The risk of transmission is greatest if the mother is also HBeAg-positive.
- Up to 90% of these infants become chronically infected if untreated.
- The risk of developing chronic HBV infection (positive for HBsAg for longer than 6 months) is inversely related to age of acquisition.
- This risk of chronic infection is 90% in children younger than 1 year. The risk is 30% for those between age 1–5 years.
- Chronic infection is associated with the development of chronic liver disease and hepatocellular carcinoma.

Clinical findings

Acute infection

- Symptoms with acute HBV infection are unusual in childhood.
- Symptomatic infection is manifested by malaise, anorexia and abdominal discomfort, which usually precedes the onset of jaundice, and occurs weeks to months after exposure.
- Raised transaminases are detected in serum, and serological markers of infection are present.
- Acute infection is rarely a severe illness, although in up to 1% of infected cases fulminant hepatic failure may occur.

Chronic infection

- HBV infection in children is important because it has high propensity to develop chronic infection.
- Factors increasing the predisposition to develop the chronic infection are some genetic factors, immunosuppression, and the age of acquisition. Perinatally infected infants have an 80–90% risk of chronic infection.
- Chronic carriers of HBV are often asymptomatic, but fatigue and anorexia may occur. The only biochemical abnormality may be mild increase in transaminase level.
- Presentation may be delayed until the onset of complications of cirrhosis and portal hypertension or with hepatocellular carcinoma.
- An acute exacerbation of hepatitis or more rapid progression of chronic disease may occur with hepatitis delta infection.

Extrahepatic manifestations

- Polyarteritis nodosa
- Glomerulonephritis (GN)
- Macular or maculopapular rash
- Arthritis
- Aplastic anemia
- Guillain-Barre syndrome

Management

Supportive measures

- Bed rest and a nutritious diet are given.
- Corticosteroids are contraindicated.

Antiviral and immunomodulatory therapy

- The aim of treatment is to eradicate replicating HBV infection in chronic carriers. This can be achieved by elimination of circulating eAg and HBV DNA and sero-conversion to eAb. Complete clearance of HBV infection by seroconversion to sAb with loss of sAg is required.
- Indications for treatment include:
    - Persistently raised serum aminotransferases.
    - Presence of HbsAg, eAg and detectable HBV DNA in serum.
    - Features of chronic hepatitis on liver biopsy.
    - **Interferon-∝2b (IFN-∝2b)** is the only agent, which has beneficial effect in eliminating the chronic HBV carriage. Recommended dose of INF-∝ is 5–10 MU/m^2 thrice weekly by subcutaneous injection for 4–6 months.
    - Oral antiviral agents (lamivudine) have been evaluated, alone and in combination with IFN, in treatment of HBV.

  - **Lamivudine** prevents replication of HBV by competitive inhibition of viral reverse transcriptase. Dose is 3 mg/kg/day for 12 months in children older than 2 years. Combination therapy with IFN may give additional benefit.
- Adefovir (a purine analog that inhibits viral replication) is approved for use in children older than 12 yrs of age.
- Peginterferon-□2 has the same mechanism of action (modulator immune and antiviral) as IFN, but is given once weekly.

Liver transplantation

- Chronic HBV-related disease is an infrequent indication for transplantation in children.

Management of a newborn

Infants born to HBsAg-negative mothers

- For all infants at birth and born to HBsAg-*negative* mothers, the 1st dose of HBV vaccine may be administered at birth.
- Subsequent doses to complete the series are given at 1 month and at 6–18 months of age.
- Post-vaccination testing of immunized infants born to HBsAg-*negative* women or with anti-HBs is not needed.

Infants born to HBsAg-positive or HBsAg-unknown mothers

- Infants born to HBsAg-positive women should receive vaccine at birth, 1–2 months, and 6 months of age. This is to prevent perinatal transmission. The 1st dose of vaccine should be accompanied by administration of 0.5 ml of HBIG (immunoglobulin) as soon after delivery as possible (within 12 hours). Effectiveness of immunoglobulin decreases rapidly with increased time after birth.
- If mother's HBsAg status is unknown, the vaccine should be administered within 12 hours of birth.
  - Mother's HBsAg status should be checked as soon as possible.
  - If she is HBsAg-positive, HBIG should be given (no later than age 1 week).
- Postvaccination testing for HBsAg and anti-HBs is recommended at 9–18 months.
  - If the result is positive for anti-HBs, the child is immune to HBV.
  - If the result is positive for HBsAg only, child has acquired the infection.
  - If the result is negative for both HBsAg and anti-HBs, a second complete hepatitis B vaccine series should be given. It is followed by testing for anti-HBs to determine if subsequent doses are needed.

Prevention

- Screening of blood donors and pregnant women.
- Use of properly sterilized needles and surgical equipment
- Vaccination of household contacts, medical personnel, and those at high risk
- Universal immunization of all newborn infants
- Vaccine is highly effective for pre-exposure prophylaxis. Post-exposure administration of hepatitis B immune globulin (0.06 ml/kg IM, given as soon as possible after exposure, up to 7 days) and initiation of vaccination are also effective.

Prognosis

- Prognosis is good, although fulminant hepatitis, chronic persistent hepatitis, or chronic active hepatitis and cirrhosis may be present in 10% of patients.
- Jaundice usually clears before 2 weeks.
- HBsAg disappears in 95% of cases when they recover clinically. Persistent asymptomatic antigenemia may occur.
- Persistence of neonatally acquired HBsAg occurs in 70–90% of infants. Presence of e antigen in the HBsAg carriers denotes a poor prognosis.
- Chronic hepatitis B disease predisposes the patient to development of hepatocellular carcinoma.

HEPATITIS C

- Hepatitis C Virus (HCV) infection, like HBV, carries a risk of progressive liver disease and hepatocellular carcinoma.
- In childhood, HCV often has iatrogenic acquisition and becomes a chronic infection.

Epidemiology

- HCV infection is the most common cause of chronic liver disease in adults. In pediatric patients, 6–19% of children achieved spontaneous sustained clearance of the virus after 6 years.
- About 170 million people worldwide have chronic HCV infection.
- HCV accounts for up to 90% transfusion-associated hepatitis. It is also the major cause of sporadic non-A non-B infection.
- About 50% of the patients have no identified risk factor.

Transmission

Parenteral transmission

- It is the most common mode of transmission.
- The risk of parenteral acquisition of HCV infection is increased in children exposed to multiple donors, either receiving multiple transfusions or by repeated infusion of pooled products.
- Illegal drug use with exposure to blood and blood products is also possible.

Vertical transmission

- Vertical transmission of HCV is common.
- It occurs in about 9% of the newborns delivered to HCV RNA-positive mothers.

- If mother is coexistent HIV-positive, the risk of transmission is increased up to 48%. The incubation period is 7–9 weeks.
- Breastfeeding is not contraindicated because the risk of HCV transmission does not seem to be significant.

Natural history

- HCV infection has a very variable outcome and rate of progression.
- In adults, 60–80% develop chronic infection.
- Acute infection is less likely to lead to chronic HCV carriage.
- Mean interval to cirrhosis is approximately 15 years for transfusion-associated disease.
- Annual incidence of hepatocellular carcinoma in those with cirrhosis is 1.4%.

Clinical findings

- Incubation period of HCV infection is from 14–160 days.
- Symptoms are present only in a minority of acute cases and include fever, malaise, nausea, abdominal discomfort and jaundice.
- Chronic infection is also usually asymptomatic or only accompanied by fatigue.

Complications

- The risk of ALF caused by HCV is low.
- The risk of chronic hepatitis is the highest of all the heptotropic viruses.
- Cirrhosis
- Hepatocellular carcinoma

Diagnosis

Serum aminotransferases

- Typically aminotransferases peak during the acute infection. A fluctuating elevation of enzymes is characteristic of chronic HCV infection; but these may be normal.

Serology (ELISA, PCR)

- Initial diagnosis of HCV infection is made following the serological detection of anti-HCV antibody (anti-HCV). The detection of anti-HCV only signifies exposure to the virus. It is not a neutralizing antibody.
- Anti-HCV is acquired passively at birth from infected mothers and cannot be used to confirm disease in the neonate for the first 15 months.

Acute/active infection

- Anti-HCV–positive
- HCV RNA–positive. (PCR)

Past infection (recovered)

- Anti-HCV–negative
- Blood PCR–negative

Chronic infection

- Anti-HCV–positive
- Blood PCR–positive

Management

- Treatment of acute HCV hepatitis is supportive.
- Chronic hepatitis caused by HCV is treated with combined interferon-∝ (3 million U/m^2 subcutaneously three times a week for 6–12 months) and ribavirin (15 mg/kg/day), with sustained response rates of 30–50%.
- The response is poorer in infections with genotype 1a or 1b and very good for genotypes 2 and 3.
- Long-acting (pegylated) interferon and oral ribavirin is more effective, with sustained viral response (SVR) rates up to 60–70%. It can be used in children older than 3 years. Better response is obtained in children under 12 years, genotype 2 and 3 and viral titres <2 million copies/ml of blood. SVR is defined as absence of viremia for 6 months after stopping treatment. Treatment is given for 48 weeks.
- ORAL regimen with sofosbuvir and simeprevir has greater chance of eradicating viral infection.
- Endstage liver disease secondary to HCV is treated with liver transplantation.
  - Reinfection after transplantation is common and is occasionally rapidly progressive.
  - Pre-and post-transplant antiviral therapy reduces the risk of reinfection.
- There is no vaccine available.
- There is no benefit from using immune globulin in infants born to infected mothers.
- Elective cesarean delivery in HCV-infected pregnant women with a high titer of circulating virus is indicated. It may lessen the risk of vertical transmission.

Prevention

- Once HCV infection is diagnosed, patients should be screened yearly with a liver ultrasound and serum ∝-fetoprotein for cirrhosis or hepatocellular carcinoma.
- There is no vaccine available.
- Vaccinating the affected patient against HAV and HBV is recommended. This will prevent from superinfection with these viruses and the increased risk of developing severe liver failure.
- Immunoglobulins are not effective.

Prognosis

- Viral titers should be checked yearly to document spontaneous remission.
- In adults, 70–80% of HCV patients develop chronic hepatitis.
- Cirrhosis develops in 20% of those with chronic infection after 10–30 years.
- HCV is the leading indication for liver transplantation in adults.

- A strong association exists between chronic HCV disease and the development of hepatocellular carcinoma after about 15 years.
- About 50% of children infected by transfusion in the first few years of life develop chronic infection.

HEPATITIS D

- Hepatitis D, or delta virus (HDV), is a defective RNA virus.
- HDV can only replicate in the presence of HBsAg, and thus HDV infection only occurs in chronic HBV carriers.
- HDV can cause an infection at the same time as initial HBV infection (co-infection) or HDV can infect a person who is already infected with HBV (super-infection).
- The route of transmission is mainly parenteral. Infection may occur at the same time or subsequent to HBV acquisition.

Diagnosis

- A diagnosis of HDV infection is made by detecting anti-HDV antibodies and HBsAg in serum.
- HDV antigen may also be detected in liver tissue by immunohistochemical techniques, and HDV RNA may be detected in serum.

Clinical findings

HDV infection in HBV carriers may:

- Be asymptomatic with complete resolution of infection
- Lead to acute hepatitis or fulminant hepatic failure.
- Lead to rapid progression of chronic hepatitis

Management

- The prevention of HBV infection and eradication of HBV chronic carriage will prevent the disease associated with HDV infection.

HEPATITIS E

- Hepatitis E Virus (HEV) is a single-stranded RNA virus.
- Transmission is by the fecal-oral route, usually by contaminated water.
- HEV epidemics occur particularly after the rainy season.
- Vertical transmission may also occur.
- The disease resembles HAV infection and is usually mild and self-limiting, especially in children.
- The frequency of secondary cases in household members is low, suggesting the virus is relatively unstable.
- Chronic liver disease and persistent viremia have not been observed.
- HEV has high fatality rate in pregnant women.

HEPATITIS G

- Hepatitis G Virus (HGV) is a transfusion-transmissible agent.
- It has a high prevalence in those at risk from parenteral acquisition and may coexist with HCV.
- Vertical transmission may also occur.
- HGV may cause acute, fulminant, and chronic hepatitis.

FULMINANT HEPATIC FAILURE

CASE

A 10 years child presents with jaundice and fever for last 2 weeks. He is lethargic and now there is bleeding from nose and mouth.

- Fulminant hepatic failure (acute liver failure) results from massive necrosis of hepatocytes or from severe functional impairment of hepatocytes.

Definition

- Biochemical evidence of acute liver injury (usually <8 week duration).
- No evidence of chronic liver disease.
- Hepatic-based coagulopathy defined as a prothrombin Time (PT) >15 sec or International normalized Ratio (INR) >1.5.

Etiology

- A complication of viral hepatitis (A, B, D, E)
- Autoimmune hepatitis
- Idiopathic causes
- Hepatotoxic drugs
- Metabolic disorders include Wilson's disease, galactosemia, hereditary tyrosinemia, and hereditary fructose intolerance

Pathogenesis

- Massive destruction of hepatocytes is due to a direct cytotoxic effect of the virus or an immune response to the viral antigens.
- Pathogenesis of hepatic encephalopathy is due to increased serum levels of ammonia, false neurotransmitters, amines, increased γ-aminobutyric acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like compounds. There is decreased hepatic clearance of these substances which causes marked central nervous system dysfunction.

Clinical findings

- Fulminant hepatic failure may be the presenting feature of acute-on-chronic liver failure.
- The disease proceeds in a rapidly fulminant course with deepening jaundice, coagulopathy, hyperammonemia, ascites, a rapidly shrinking liver, and progressive coma.
- A rapid decrease in liver size without clinical improvement is a bad sign.

Diagnosis

- Elevated serum bilirubin levels (usually >15–20 mg/dL)
- Sustained very high AST and ALT (>3000 U/L) that may decrease terminally

- Low serum albumin
- Hypoglycemia
- Prolonged prothrombin time and INR
- Blood ammonia levels become elevated, whereas blood urea nitrogen is often very low
- Hyperpnea is frequent, and mixed respiratory alkalosis and metabolic acidosis are present

Management

- Treatment of cause (if known) should be started immediately:
    - *N*-acetylcysteine for acetaminophen poisoning
    - Acyclovir for herpes simplex virus infection
    - Lamivudine for HBV infection
    - Prednisone for autoimmune hepatitis
- If cause is not known, management of fulminant hepatic failure is mainly supportive.
- No treatment is available to reverse hepatocyte injury or to improve hepatic regeneration.
- Mechanical ventilation and supplemental oxygen is needed in advanced coma.
- Electrolyte and glucose solutions should be given intravenously to maintain urine output, to correct or prevent hypoglycemia, and to maintain normal serum electrolyte concentrations especially potassium.
- Coagulopathy is treated with parenteral administration of vitamin K, infusion of fresh-frozen plasma, cryoprecipitate, and platelets.
- Plasmapheresis and hemodialysis may help stabilize a patient while awaiting liver transplantation.
- Orthotopic liver transplantation may be lifesaving in advanced stages of hepatic coma.

Prognosis

- The prognosis depends on the cause of hepatic failure and depth of coma.
- The prognosis is poor in patients with liver necrosis and multiorgan failure.

HEPATIC ENCEPHALOPATHY

CASE

A 9-year-old boy presents with ***jaundice*** for last 10 days. Now, he has ***impaired consciousness***. He has fever and vomiting. On examination, there is ascites and he is in coma. On investigations, there is ***hypoglycemia*** and ***liver function tests*** are ***raised***.

Definition

- It is defined as the deterioration of conscious level secondary to impaired liver functions. It may be due to acute as well as chronic liver disease.
- Acute insult is fulminant hepatic failure, which is defined as severe liver disease with onset of hepatic encephalopathy within 8 weeks after initial symptoms.
- Chronic insult is progressive liver disease with cirrhosis.

Table 12.6: Etiology of hepatic encephalopathy.

Etiology	***Disease***
Infectious	HAV, HBV, non-A-G virus, herpesvirus, sepsis, echovirus, adenovirus.
Drugs	Valproate, isoniazid, paracetamol, carbamazepine, halothane.
Metabolic	Galactosemia, Wilson's disease.
Autoimmune	Autoimmune hepatitis.
Ischemia	Severe asphyxia, congenital heart disease, myocarditis.
Others	Malignancy, toxins.

Pathogenesis

- Clinically, acute hepatic encephalopathy is defined as any brain dysfunction that occurs as a result of acute hepatic dysfunction and may be exacerbated by sepsis, GIT bleeding, electrolyte disturbances or sedation, particularly benzodiazepine administration.

Table 12.7: Clinical stages of hepatic encephalopathy

Stage	**Clinical manifestations**
I (prodrome)	• Mild intellectual impairment • Disturbed sleep-awake cycle • Trouble drawing figures, performing mental tasks • EEG normal
II (impending coma)	• Drowsiness, confusion, inappropriate behavior, disorientation, mood swings • Asterixis, fetor hepaticus, incontinence • EEG generalized slowing, q waves
III (stupor)	• Drowsy, unresponsive to verbal commands, markedly confused delirious, hyperreflexia, positive Babinski sign • EEG markedly abnormal, triphasic waves
IV (coma)	• Coma • IVa-responds to noxious stimuli • IVb-no response • Areflexia, no asterixis • Flaccidity. • EEG markedly abnormal, bilateral slowing, d waves, electric-cortical silence

- Acute hepatic encephalopathy usually evolves over days through definable stages. It may progress rapidly, with coma developing within hours of the earliest detectable signs.

- **Metabolic factors** involved in hepatic encephalopathy are:
  - **Hypoglycemia** due to impaired glycogenolysis and glyconeogenesis, may alter conscious level.
  - **Hypoalbuminemia** leads to decreased oncotic pressure and shifting of intravascular fluids to extravascular space. There is decreased cerebral blood flow causing cerebral hypoxia and increased brain sensitivity.
  - **Hypokalemia** occurs in acute hepatic failure because of vomiting, nasogastric tube suction, diuretics, and hyperaldosteronism. Hypokalemia leads to alkalosis and in alkalosis, there is increased ammonia level, which rapidly diffuses across blood brain barrier.
  - **Acid-base imbalance** occurs due to accumulation of organic acids, leads to diffusion of ammonia into cell.
- Encephalopathy is an essential component in the diagnosis of fulminant hepatic failure; by definition it occurs in 100% of patients. It results from an indirect effect of hepatocyte failure on the function of the brain. Hepatocyte dysfunction has progressed to a point following which the liver fails to produce appropriate amounts of neuroregulatory substances and/or fails to eliminate neurotoxins, which result in brain dysfunction. Main neurotoxins involved are ammonia, glutamine, short-chain fatty acids, amino acids, mercaptans, octopamine, and Gammaaminobutyric Acid (GABA). GABA produces coma, which is reversed by a benzodiazepine antagonist flumazenil. Cerebral intoxication by intestinal nitrogenous contents occurs through portal-systemic shunting. No neuropathological abnormalities associated with acute hepatic encephalopathy are reversible.

Table 12.8: Precipitating factors of hepatic encephalopathy (coma).

- Infections
- GIT bleeding
- High protein diet
- Constipation
- Sedatives
- Paracentesis
- Hypokalemia
- Trauma/surgery

Clinical findings

- Fever
- Anorexia
- Abdominal pain
- Vomiting
- Deep jaundice (absent in Reye's syndrome)
- Petechiae/bruises
- Ascites
- Fetor hepaticus
- Liver palpable/impalpable
- Peripheral stigma of chronic liver disease
- CNS involvement like irritability, poor feeding, minor disturbances of consciousness or motor function. Asterixis may be present in older children. Patient may become confused, combative, and rapidly progress to deeper stages of coma.

Diagnosis

- **Complete blood count** (CBC) with platelets: TLC (total leukocyte count) may be raised due to infection or decreased due to aplastic anemia. Platelets are deceased due to consumption and reduced production.
- Marked conjugated **hyperbilirubinemia**.
- **Serum aminotransferases** (ALT, AST) may be very high (>1000 iu/l).
- **Plasma ammonia** is usually 2–8 times elevated (>100 iu/l).
- **Serum albumin** is decreased.
- **Serum creatinine** may be elevated secondary to renal complications.
- **Blood urea** may be high (renal dysfunction, increased production from blood in the GI tract, dehydration) or low (failure of hepatic synthesis).
- **Hypoglycemia** may be present and difficult to correct.
- **Arterial blood gas analysis** may show a wide spectrum of abnormalities from respiratory alkalosis to mixed respiratory and metabolic acidosis, usually in association with hypoxemia.
- **Electrolyte abnormalities** hypokalemia, hyponatremia) are associated with vomiting and dehydration.
- **Coagulation profiles** demonstrate deficiencies of clotting factors and often evidence of consumptive coagulopathy.
- **Viral markers** are determined to rule out infectious cause.
- **Abdominal ultrasonography** to see liver parenchyma.
- **Electroencephalography (EEG)** to determine stages of encephalopathy.

Management

General measures

- Admit the patient in intensive care unit
- Pass intravenous line
- Supplemental oxygen is given
- Monitoring of vital signs one hourly.
- Pass nasogastric tube for gastric lavage.
- Catheterize the patient for urine output record.
- Intravenous fluids are given.
- Strict intake output record should be established to determine fluid and renal status.

- CNS monitoring like baseline EEG to determine stage of coma and CT scan brain to determine cerebral edema should be done.

Specific treatment

- There is no specific therapy to reverse hepatocyte injury except hepatic replacement.

Prevention and management of hypoglycemia

- Severe hypoglycemia (blood glucose <40 mg/dl) develops in the majority of children. It may lead to CNS impairment and other organ dysfunction.
- Frequent bedside monitoring of blood glucose concentrations (every 2–4 hours).
- IV administration of glucose (10–50% dextrose) is required to prevent hypoglycemia.
- Profound refractory hypoglycemia carries a grave prognosis, and may lead to imminent death of the patient.

Prevention and management of coagulopathy and hemorrhage

- Profound disturbances in hemostasis develop secondary to failure of hepatic synthesis of clotting factors.
- Prolongation of PT (prothrombin time) is the most sensitive measure of hepatic synthesis of clotting factors.
- Bleeding from needle puncture sites is common, while pulmonary or intracranial hemorrhage may be terminal events.
- Coagulopathy should be corrected with fresh frozen plasma (FFP), cryoprecipitate and platelets as needed.
- In general, mild to moderate coagulopathy (PT <30 second) requires no therapy except support for procedures.
- Marked coagulopathy (PT >40 second) should be corrected (10 ml/kg of FFP every 6 hours) to prevent the risk of bleeding, particularly intracranial hemorrhage. If major bleeding occurs, additional attempts should be made to correct coagulation using 15–20 ml/kg FFP every 6 hours, or continuous infusions at a rate of 3–5 ml/kg/hour.
- Vitamin K is given.

Prevention of GIT hemorrhage

- GIT hemorrhage may be life threatening due to gastritis or stress ulceration.
- High-dose H_2-antagonists (ranitidine 1–3 mg/kg 8 hourly) or H-pump inhibitors (omeprazole 1 mg/kg/day) should be administered IV and sucralfate (1–2 g 4 hourly) may be given by nasogastric tube to reduce upper GIT bleeding.

Dietary management

Therapy to reduce ammonia production or accumulation is indicated. The essential components of therapy are:

- Restriction of dietary protein. Protein intake should be limited to 0.5–1 g/kg/day and may be administered orally or parenterally to limit the production of ammonia.
- Enteral antibiotics. Neomycin (50–100 mg/kg/day) is used to prevent ammonia production by bacteria.
- Enteral lactulose (1–2 ml/kg every 4–6 hour).
- Caloric intake is maintained in the early stages with glucose polymers and supplemented by infusion of 10% dextrose solution, while frequently monitoring blood glucose.
- Sedation is not usually needed, except in violent patients to prevent self-injury. Benzodiazepines are contraindicated. Haloperidol, midazolam, or phenytoin may be used.
- Flumazenil (a benzodiazepine antagonist) may produce temporary reversal of hepatic encephalopathy.

Treatment of cerebral edema

- Brain death associated with cerebral edema is the most frequent cause of death in fulminant hepatic failure.
- Key strategy is fluid restriction (<75% of maintenance), maintaining circulating volume with colloid.
- IV infusion of mannitol (0.5 g/kg every 4–6 hour) controls acute increases in intracranial pressure.
- Elective hyperventilation (PCO_2<3.5 kPa) may have a temporary effect in reducing ICP (intracranial pressure).

Electrolyte and acid-base disturbances

- Disturbances in sodium homeostasis (hyponatremia and/or hypernatremia) are observed in almost all children. Hyponatremia is more common, despite sodium retention by the kidney. A total sodium intake of 0.5–1.0 mmol/kg/day is usually adequate.
- Hypocalcemia and hypomagnesemia frequently occur and should be corrected.
- Acid-base disturbances are common and may be secondary to liver failure, sepsis or the underlying disease.

Treatment of renal dysfunction

- Renal insufficiency may be present in up to 75% of children. It is due to prerenal uremia, acute tubular necrosis and functional renal failure. Hepatorenal syndrome is characterized by low urine output azotemia and low urine sodium content.
- Aim of management is to maintain circulating volume to prevent prerenal hypovolemia and ensure urine output is more than 0.5 ml/kg/hour. A fluid challenge (10 ml/kg) may be successful if there is no fluid overload. In case of fluid overload, frusemide (1–2 mg/kg IV) may be effective. Established renal failure requires hemodialysis or filtration for fluid overload.

Treatment of ascites

- There is excessive peritoneal fluid in most patients due to acute portal hypertension, from lobular collapse, vasodilatation, poor vascular integrity and reduced oncotic pressure.
- Treatment includes correction of oncotic pressure with 4.5% or 20% albumin infusion, and general fluid management.

Treatment of secondary bacterial and fungal infections

- About 50% of children will develop significant infection, which may be due to impairment of cellular and humoral immune systems. Most common organisms are Gram-positive e.g. *Staphylococcus aureus, S. epidermidis, and streptococci*. Occasionally, Gram-negative bacteria or fungal infection are present. UTI, particularly from indwelling catheters, and pulmonary infection, particularly in ventilated children, are common.
- Broad-spectrum antibiotics should be given prior to the suspicion of sepsis, as the signs may be subtle. Amoxycillin (25 mg/kg/dose 8 hourly), cefuroxime (20 mg/kg/dose 8 hourly), and/or metronidazole (8 mg/kg/dose 8 hourly), if there is a suspicion of anaerobic infection, are suitable first-line drugs. Aminoglycoside antibiotics should be avoided, if possible, because they can contribute to renal failure.

Treatment of aplastic anemia

- Bone marrow failure is a fatal complication of sporadic NA-G hepatitis, parvovirus B19, and HSV-VI fulminant hepatic failure.
- Bone marrow transplantation, administration of granulocyte colony stimulating factor or granulocyte/macrophage stimulating factor may be tried.

Liver transplantation

- Liver transplantation is indicated in all children who develop a stage III or IV hepatic coma (mortality in this group is more than 70%).
- Transplantation is indicated in all forms of fulminant hepatic failure (viral hepatitis, paracetamol overdose, Wilson's disease, etc.).
- Development of irreversible brain damage is a major contraindication to transplantation.

Prognosis

- Depends on:
    - Cause of hepatic failure
    - Staging of encephalopathy
- Children under 10 years of age have the worst overall prognosis, which varies according to etiology.
- Patients with fulminant hepatitis A have the best overall survival (68%). Survival rates for other etiologies are less.
- Stage IV has poor prognosis.
- Poor prognostic factors are:
    - Jaundice >7 days before onset of encephalopathy
    - PT >50 seconds
    - Bilirubin >17.5 mg/dl

AUTOIMMUNE HEPATITIS

CASE

A 12-year-old girl presents with ***jaundice***. On examination, she is jaundiced and has ***spider nevi*** on the face and upper chest. On investigations, ***bilirubin and ALT*** are ***elevated*** with ***positive antinuclear*** and ***antismooth muscle antibodies***.

- Autoimmune hepatitis is a chronic hepatic inflammatory process characterized by:
    - Elevated serum aminotransaminase concentrations
    - Liver associated serum autoantibodies
    - Hypergammaglobulinemia

Clinical findings

- Fever
- Malaise
- Recurrent or persistent jaundice
- Skin rash
- Arthritis
- Amenorrhea
- Gynecomastia
- Acne
- Pleurisy, pericarditis.
- Ulcerative colitis may be present in these patients.
- Asymptomatic hepatomegaly or splenomegaly may be present.
- There may be acute liver failure.
- Cutaneous signs of chronic liver disease (e.g. spider angiomas, palmar erythema, and digital clubbing).
- Hepatic encephalopathy.

Diagnosis

- LFTs show moderate elevations of serum bilirubin, AST, ALT (and not serum alkaline phosphatase).
- Serum albumin may be low.
- Serum □-globulin levels are strikingly elevated (2–6 g/dL).
- Low levels of C3 complement.
- Positive Antinuclear Antibodies (ANA), Anti-Smooth Muscle Antibodies (ASMA), Anti-Liver-Kidney Microsomal (ALKM) antibodies, or Anti-Soluble Liver Antibodies (ASLA).
- Absence of liver markers.
- Liver biopsy: Histologic examination of liver biopsy specimens shows loss of the lobular limiting plate, and interface hepatitis ("piecemeal" necrosis). Cirrhosis may be present at diagnosis in up to 50% of patients.

Management

- Corticosteroids (prednisone, 2 mg/kg/day). It decreases the mortality rate during the early and active phase of the disease.
- Azathioprine or 6-mercaptopurine (6MP), 1–2 mg/kg/day.
- Steroids are reduced over a 3-to 12-month period, and azathioprine is continued for 1–2 years.
- Liver biopsy is performed after 1–2 years, if inflammation persists, then azathioprine is continued.
- Complications of portal hypertension (bleeding varices, ascites, spontaneous bacterial peritonitis, and hepatopulmonary syndrome) require specific therapy.
- Liver transplantation is indicated when disease progresses to cirrhosis.

Prognosis

- The overall prognosis for autoimmune hepatitis may be improved with early therapy.
- Survival for about 10 years is common even in the presence of cirrhosis.
- 20–50% children with autoimmune hepatitis require liver transplantation.

CIRRHOSIS

CASE

A 12-year-old boy presents with non-specific fatigue, poor appetite and mild jaundice. On examination, there is hard liver palpable 2 cm below right costal margin. There is also splenomegaly.

Definition

- Cirrhosis is a histologically defined condition of the liver characterized by:
    - Diffuse hepatocyte injury and regeneration
    - An increase in connective tissue (fibrosis)
    - Disorganization of the lobular and vascular architecture

Main points

- Cirrhosis may be micronodular or macronodular.
- Typically, the entire liver is involved.
- There is vascular distortion leading to increased resistance to blood flow. This produces portal hypertension and its complications.
- There are two types of cirrhosis:
    1. Postnecrotic cirrhosis
    2. Biliary cirrhosis
- Main causes of postnecrotic cirrhosis are:
    - Acute or chronic liver disease (e.g. idiopathic neonatal giant cell hepatitis; viral HBV, HCV, autoimmune hepatitis, drug-induced hepatitis)
    - Certain inborn errors of metabolism (Wilson's disease, galactosemia, tyrosinemia, ∝1-antitrypsin deficiency)
- Main causes of biliary cirrhosis are:
    - Congenital abnormalities of the bile ducts (biliary atresia, choledochal cyst)
    - Cystic fibrosis
    - Hypoplasia of intrahepatic bile ducts
    - Primary sclerosing cholangitis
- Cirrhosis may follow a hypersensitivity reaction to drugs.

Clinical findings

- General malaise
- Loss of appetite
- Failure to thrive
- Nausea
- Easy bruising
- Jaundice may or may not be present
- Ascites
- Gastrointestinal hemorrhage
- Hepatic encephalopathy
- Hepatosplenomegaly (variable)
- Spider angiomas
- Warm skin
- Palmar erythema
- Gynecomastia
- Digital clubbing
- Pretibial edema
- Irregularities of menstruation and amenorrhea in girls
- Jaundice, dark urine, pruritis, xanthoma, and hepatomegaly also present in biliary atresia

Diagnosis

- Mild abnormalities of aminotransferases (AST, ALT)
- Decreased level of albumin
- A variable increase in the level of gamma globulins.
- Prothrombin Time (PT) is prolonged. It is unresponsive to vitamin K administration
- In peripheral blood film, there are burr and target red cells
- In case of hypersplenism, there is anemia, thrombocytopenia, and leukopenia
- In biliary cirrhosis, there is elevated conjugated bilirubin, bile acids, gamma-glutamyl transpeptidase, alkaline phosphatase, and cholesterol
- Hepatic ultrasound or CT scan: There is abnormal hepatic texture and nodules. Abnormalities of biliary tree are apparent in biliary cirrhosis. Bile duct size and flow is determined
- Liver biopsy:
    - Regenerating nodules and surrounding fibrosis
    - Canalicular and hepatocyte cholestasis is seen in biliary cirrhosis

Complications

- Progressive nutritional disturbances
- Hormonal disturbances
- Portal hypertension and its complications
- Hepatocarcinoma

Management

- At present, there is no proven medical treatment for cirrhosis.
- Whenever a treatable condition is diagnosed (e.g. Wilson's disease, galactosemia) or a causative agent is eliminated (drugs, toxins), disease process can be altered. In some cases, regression of fibrosis may be noted.
- In autoimmune hepatitis, immunosuppressive treatment is given.
- Biliary tract abnormalities can be treated surgically.
- Liver transplantation is the ultimate treatment.

Prognosis

- Prognosis is poor.
- Patients usually survive less than 1 year who have:
    - A rising bilirubin
    - A vitamin K-resistant coagulopathy
    - Diuretic refractory ascites
- Causes of death are generalized hemorrhage, sepsis, or cardiovascular arrest.

PORTAL HYPERTENSION AND VARICES

CASE

A 7-year-old boy is a diagnosed case of ***chronic liver disease***. Now, he presents with a massive ***hematemesis***. There is a history of exchange transfusion in neonatal age. On examination, he is pale and in shock. Blood pressure is not recordable. There is ***splenomegaly*** but liver is not palpable. Ascites is also present.

Definition

- It is defined as an increase in the portal venous pressure to more than 10–12 mmHg (normal 7 mmHg).

Classification

- Portal hypertension is most commonly a result of cirrhosis.
- Portal hypertension may be divided into:
    - Extrahepatic
    - Intrahepatic

Main causes

Extrahepatic portal hypertension

- Portal vein agenesis, atresia, stenosis
- Portal vein thrombosis or cavernous transformation
- Splenic vein thrombosis
- Increased portal flow
- Arteriovenous fistula

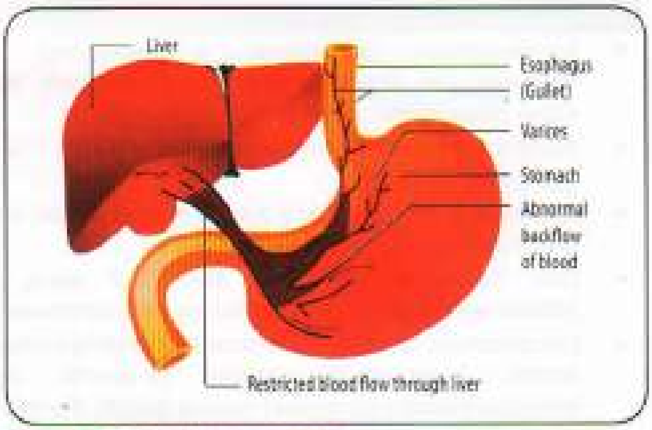

Liver
Esophagus (Gullet)
Varices
Stomach
Abnormal backflow of blood
Restricted blood flow through liver

Figure 12.8 Portal hypertension.

Intrahepatic portal hypertension

- Hepatocellular disease
- Acute and chronic viral hepatitis
- Cirrhosis
- Wilson's disease
- α_1-antitrypsin deficiency
- Glycogen storage disease type IV
- Hepatotoxicity
- Methotrexate
- Parenteral nutrition
- Biliary tract disease
- Extrahepatic biliary atresia
- Cystic fibrosis
- Choledochal cyst
- Budd-Chiari syndrome

Clinical findings

- Splenomegaly is the most constant physical sign.
- Recurrent episodes of abdominal distension due to ascites.
- Hematemesis and melena due to rupture of esophageal varices.

Diagnosis

- Blood smear examination
- Hepatic serologies
- Liver function tests: In extrahepatic portal hypertension, liver function tests are generally normal.
- Upper endoscopy will reveal varices in symptomatic patients.
- USG assist in defining the vascular anatomy. Doppler flow USG may demonstrate the deviation of flow within the portal system. The pattern of flow correlate with severity of cirrhosis and encephalopathy. Hepatopetal flow is more likely to be associated with variceal bleeding.
- Selective angiography of celiac axis, superior mesentreric artery and splenic veins may be useful in precise mapping of extrahepatic vascular anatomy.
- Endoscopy is necessary to detect esophageal varices and for injecting sclerosing agents.

- Liver biopsy

Differential diagnosis

- All causes of splenomegaly (infections, ITP, cirrhosis)
- All causes of cirrhosis
- All causes of hematemesis or melena

Complications

- Bleeding from esophageal varices
- Hypersplenism
- Hepatic failure

Management

- There is no definitive treatment of non-cirrhotic portal hypertension.
- Preferred option is aggressive medical treatment.
- Withdrawal of the suspected offending agent may increase the chances of recovery.
- In cirrhotic patients, liver transplantation should be considered.
- For bleeding esophageal varices:
  - Fluid resuscitation initially in the form of crystalloid followed by replacement of red blood cells.
  - NG tube should be placed to monitor for ongoing bleeding.
  - Endosclerosis or variceal ligation
  - Octreotide ($30\ \mu g/m^2$/hour IV)
  - Pediatric Sengstaken-Blackmore tube
  - Surgical variceal ligation
  - Selective venous embolization
  - Propranolol: It lowers cardiac output and portal perfusion, so reduces incidence of variceal bleeding.
  - Transjugular Intrahepatic Portosystemic Shunt (TIPS).
  - Orthotopic Liver Transplantation (OLT) is a much better therapy of intrahepatic disease.
  - Treatment of ascites

Prognosis

- Portal hypertension secondary to intrahepatic disease has a poor prognosis.
- Prognosis is better in patients managed medically with supportive therapy as compared to patients managed surgically.

LIVER ABSCESS

CASE

A 5-year-old child presents with ***high grade fever*** and ***diarrhea*** for last two weeks. He is fully vaccinated. On examination, he is toxic. Temperature is 103°F. There is tender liver of 5 cm below right costal margin (***hepatomegaly***).

- Liver abscess is usually solitary and located in the right hepatic lobe.
- Multiple pyogenic liver abscesses are associated with severe sepsis.

Causes

- Intestinal bacteria: Pyogenic liver abscesses are commonly caused by intestinal bacteria seeded in liver via the portal vein from infected viscera. Some important causes are:
  - Intraabdominal sepsis, appendicitis, omphalitis, inflammatory bowel disease.
  - Cholangitis
  - Generalized sepsis
  - Chronic granulomatous disease
  - Amebic dysentery
- Common organisms are:
  - *Staphlococcus aureus*
  - *E. coli*
  - *Salmonella*
  - *Anaerobic organisms*
  - *Entamoeba histolytica* invasion occurs via the large bowel
  - *Toxocara canis*

Clinical findings

- Non-specific symptoms of fever, chills, malaise, abdominal pain.
- Weight loss is common.
- There may be shaking chills but jaundice is rare.
- Constant dull pain over an enlarged, tender liver.
- Elevated hemi-diaphragm with reduced or absent respiratory excursion (confirmed by fluoroscopy) on right side.
- There may be cough, dyspnea, and shoulder pain if abscess ruptures into the right chest.
- In about 30% of cases, right lower lobe of lung has consolidation.

Diagnosis

- CBC: Leukocytosis, anemia, raised ESR.
- LFTs: May be normal or there may be mild elevation of transaminases and alkaline phosphatase.
- Blood culture may be positive in up to 60% of patients.
- Ultrasonography.
- CT scan.
- Direct hemagglutination test: It is positive in more than 95% of patients with amebic liver disease.
- Examination of material obtained by needle aspiration using USG guidance is usually diagnostic and differentiates pyogenic and amebic abscesses.

Differential diagnosis

- Hepatitis
- Hepatoma
- Hydatid cyst

- Gallbladder disease
- Biliary tract infections
- Sub-phrenic abscess
- Empyema
- Pneumonia

Complications

- Spontaneous rupture of the abscess
- Metastatic hematogenous spread to the lungs and the brain
- Amebic liver abscess may be secondarily infected with bacteria in 10–20% of cases

Management

- USG guided aspiration or drainage of abscess
- Antibiotic therapy is given especially in a case with multiple liver abscesses. Antibiotics are given according to culture/sensitivity. For staphalococcus aureus, naficillin, oxacillin, or vancomycin may be given.
- Metronidazole (35–50 mg/kg in 3 divided doses for 10 days) in a case of amebic abscess. In severe case dehydroemetine (1.0–1.5 mg/kg/day IM in 2 divided doses for 5 days) and chloroquine (10 mg/kg/day for 2–3 weeks) are given.
- Surgical treatment: If abscess ruptures outside the liver capsule, or if there is enterohepatic fistula.
- Abscess cavity usually resolves over 3–6 months.

Prognosis

- Unrecognized and untreated liver abscess is fatal.
- Cure rate is 90% with proper treatment.

ASCITES

CASE

Budd-Chiari syndrome: A 4-year-old child presents with history of ***gross distension of abdomen*** and ***hemetemesis*** for 3 months. On examination, he is a sick looking child with grossly distended abdomen. There are prominent veins ***all over the abdomen and chest***. Jugular venous pressure ***(JVP)*** is ***raised***. There is also tender ***hepatomegaly*** and ***ascites***.

Definition

- Ascites is the accumulation of abnormal amount of fluid in the peritoneal cavity.

Etiology

Hepatic causes

- Cirrhosis
- Portal vein obstruction
- Fulminant hepatic failure
- Budd-Chiari syndrome
- Lysosomal storage disease

Renal causes

- Nephrotic syndrome
- Obstructive uropathy
- Perforation of urinary tract
- Peritoneal dialysis

Cardiac causes

- Heart failure
- Constrictive pericarditis

Infectious causes

- Abscess
- Tuberculosis

Gastrointestinal causes

- Infarcted bowel
- Perforation
- Protein-losing enteropathy

Neoplastic causes

- Lymphoma
- Neuroblastoma

Gynecologic causes

- Ovarian tumors
- Ovarian torsion, rupture

Pancreatic causes

- Pancreatitis
- Ruptured pancreatic duct

Miscellaneous causes

- Systemic lupus erythematosus
- Ventriculoperitoneal shunt
- Chylous ascites

Pathogenesis

- The presumed initial factor in the development of ascites in case of congestive heart failure is increased hydrostatic pressure.
- In children with nephrotic syndrome, protein-losing enteropathy, or malnutrition, the associated hypoalbuminemia results in a decreased oncotic pressure. These alterations in Starling forces cause fluid to move from the intravascular space to the extravascular space. When the rate of extravascular fluid production exceeds the ability of the lymphatic system to reabsorb this fluid and transport it back to the vascular system, the fluid accumulates in the peritoneal cavity resulting in ascites.
- Intrahepatic venous obstruction caused by hepatic inflammation and scarring, increases hydrostatic pressure in the hepato-splanchnic venous system. Increased hydrostatic pressure, in conjunction with a low oncotic pressure due to decreased hepatic protein synthesis, forces fluid out of the hepatosplanchnic vascular space into the peritoneal cavity. The intravascular volume is decreased, which stimulates the rennin-angiotensin-aldosterone system to retain

renal sodium to replenish the intravascular volume. It also causes secretion of ADH (antidiuretic hormone). Sodium retention increases the hydrostatic pressure in the hepato-splanchnic circulation, which promotes the accumulation of more ascitic fluid, establishing a vicious cycle.

Clinical findings

- Characteristic clinical finding of ascites is abdominal distension.
- Other physical findings include bulging flanks, protrusion of the umbilicus, and scrotal swelling.
- Patients with portal hypertension may have prominent abdominal veins.
- When the ascites is massive, patient's condition is obvious. When ascites is mild to moderate, three physical signs (flank dullness, shifting dullness, and fluid thrill) can help detect ascites.
- Patients with ascites secondary to cirrhosis may have physical signs of chronic liver disease, such as jaundice, spider naevi, splenomegaly, palmar erythema, caput medusae, esophageal varices, and peripheral edema.
- Cardiac and chest examination is also important.
- A physical assessment of nutritional status should be performed. Patients with ascites may be compromised nutritionally because of the underlying disorder that caused the ascites.

Diagnosis

- Blood count
- Liver Function Tests (LFTs)
- Serum protein
- Albumin/globulin ratio
- Urine routine examination
- Urinary protein
- X-ray chest: There may be cardiomegaly.
- Abdominal ultrasonography: USG can demonstrate as little as 150 ml of fluid. It can differentiate free from loculated fluid.
- Analysis of ascitic fluid: Ascitic fluid for diagnostic evaluation is obtained by abdominal paracentesis. **Transudative ascitic fluid** is clear or straw colored, with total protein concentrations less than 2.5–3.0 gm/dl or less than half the plasma total protein concentrations. The leukocyte count is less than 250–500 cells/mm^3, less than one third of the cells are neutrophils. Gram stain and cultures reveal no organisms. **Exudative ascitic fluid** is secondary to inflammation of the peritoneum or abdominal viscera (i.e. peritonitis, pancreatitis). Exudative peritoneal fluid is usually turbid or cloudy. Protein content is elevated (>2.5 gm/dl). LDH (lactic dehydrogenase) is elevated; pH is low (<7.31). The single best predictor of peritonitis is a neutrophil count greater than 250 cells/mm^3.

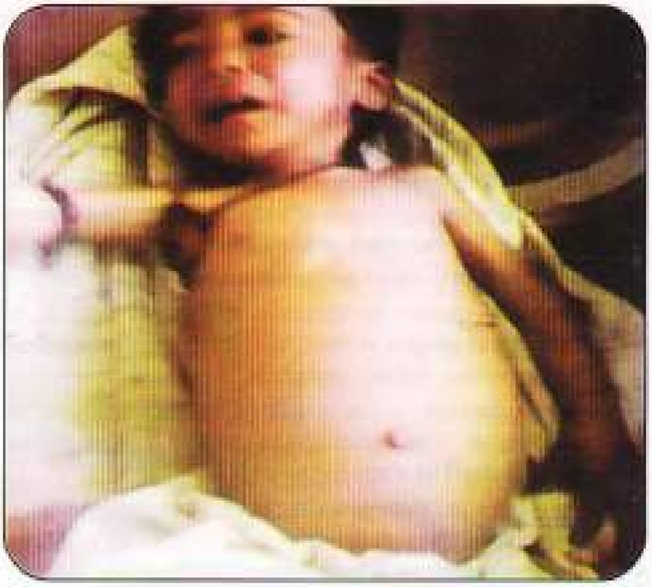


Figure 12.9 Ascites in a child with chronic liver diseases.

Management

- The initial therapy must be directed at the underlying disorder, after which the ascites may be treated.
- Medical treatment consists of primarily nutritional support and diuretic therapy.
- Salt restriction (1–2 mEq/kg/day) is the mainstay of nutritional therapy in the treatment of ascites and should be instituted immediately.
- Diuresis should be instituted gradually with diuretics to avoid hypovolemia.
    - ○ Spironolactone (3–5 mg/kg/day)
    - ○ Frusemide (1–2 mg/kg/day)
- IV albumin (0.5–1.0 g/kg/dose) can be infused with frusemide to achieve a more rapid diuresis in patients who are acutely symptomatic.
- Many patients do not respond to nutritional and diuretic therapy. They may be considered for following procedures:
    - ○ Peritono-venous shunts
    - ○ Transjugular Intrahepatic Portosystemic Shunt (TIPS)
    - ○ Orthotopic Liver Transplantation (OLT)
- Spontaneous bacterial peritonitis may be complication of ascites and should be considered and treated if fever and abdominal pain are present.

WILSON'S DISEASE (HEPTOLENTICULAR DEGENERATIO

CASE

A 10-year-old boy presents with difficulty in speech, abnormal posturing and ***deteriorating school performance***. Further investigations reveal ***Kayser–Fleischer rings*** on slit lamp examination. On investigations serology of HBV, HCV and HDV are negative.

- It is an autosomal recessive disorder of copper metabolism that occurs in 1:30,000 live births.
- The defective gene is on chromosome 13, which encodes ATP7B required for biliary copper excretion.
- Wilson's disease should be considered in all children older than 3 years of age with evidence of liver disease or with neurologic signs in older children (9–10 years). Girls are 3 times more prone to have liver disease.
- A family history is often present.
- It causes copper to accumulate progressively in the liver, basal ganglia of the brain, Descemet's membrane in the cornea, kidney and bone.
- Organ damage is the result of toxicity from copper deposition. The accumulated copper causes oxidant (free-radical) damage to the organs.
- Levels of the copper-binding protein ceruloplasmin are low in 80–95% of patients.

Clinical findings

- **Liver disease** is the primary mode of presentation in pediatric patients. Liver disease rarely is clinically evident before 5 years of age. The presentation may include an episode of acute hepatitis, fulminant hepatitis, chronic hepatitis, or cirrhosis.
- **Neurological symptoms** include deterioration of school performance, behavior changes, drooling, abnormal posturing of limbs and trunk (dystonic posturing), loss of normal speech (dysarthria), deterioration of hand-writing, gait abnormality, and later fits. These usually occur when the child is older than 10 years of age.
- **There may be:**
    - Coombs-negative hemolytic anemia
    - Renal involvement (usually a Fanconi-like syndrome)
    - Corneal deposition of copper in descement's membrane

Diagnosis

- **Kayser–Fleischer (KF) rings** are pathognomonic when present (seen by slit lamp examination as brown band at the junction of iris and cornea). KF ring may be absent (up to 50%) in young patients with liver disease but are always present in patients with neurologic symptoms (90%).
- **Ceruloplasmin level** is usually low (<20 mg/dl). A level exceeding 30 mg/dl excludes Wilson's disease.
- **Elevated urinary copper excretion** (>100 mg/24 hours). Penicillamine challenge test: Penicillamine is given in dose of 500 mg orally and then same dose in repeated after 12 hours, during 24 hours urine collection. If urine copper is >1000 mg/24 hours it is diagnostic of Wilson's disease.
- Quantification of liver copper by **liver biopsy** (levels are greater than 250 ug/g dry weight of liver).
- **Coomb's negative hemolytic anemia** may be present.

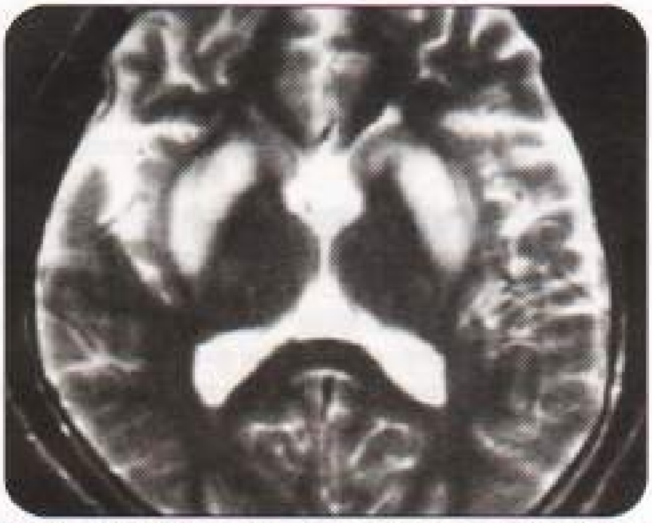


Figure 12.10 MRI brain scan showing degeneration in Wilson's disease.

Differential diagnosis

- Acute viral hepatitis
- α_1-antitrypsin deficiency
- Autoimmune hepatitis
- Indian childhood cirrhosis
- Drug-induced hepatitis

Complications

- Progressive liver disease
- postnecrotic cirrhosis
- Hepatic coma
- Progressive neurologic degeneration
- Death in untreated patient
- Acute hemolytic disease may result in acute renal failure and profound jaundice (fulminant hepatitis)

Management

- Food with high copper content (chocolate, nuts, dry fruits, mushrooms) should be avoided.
- Lifelong treatment with chelating agent D-pencillamine is necessary. Dose is 20 mg/kg/day.
- Trientine (20 mg/kg/day) is another copper chelating agent.
- Zinc acetate 20–50 mg orally three times daily reduces copper absorption.
- Vitamin B_6 (25 mg) is given to prevent optic neuritis due to pencillamine.
- Liver transplantation in cases of cirrhosis.
- Screening and treatment of sibling is also important.

Prognosis

- The prognosis is excellent with early treatment.
- The prognosis of untreated Wilson's disease is poor.
- Fulminant hepatitis has poor prognosis.
- Neurological damage is permanent.
- All siblings should be immediately screened. Homozygote siblings should be given treatment with copper chelation or zinc acetate therapy, even if they are asymptomatic.

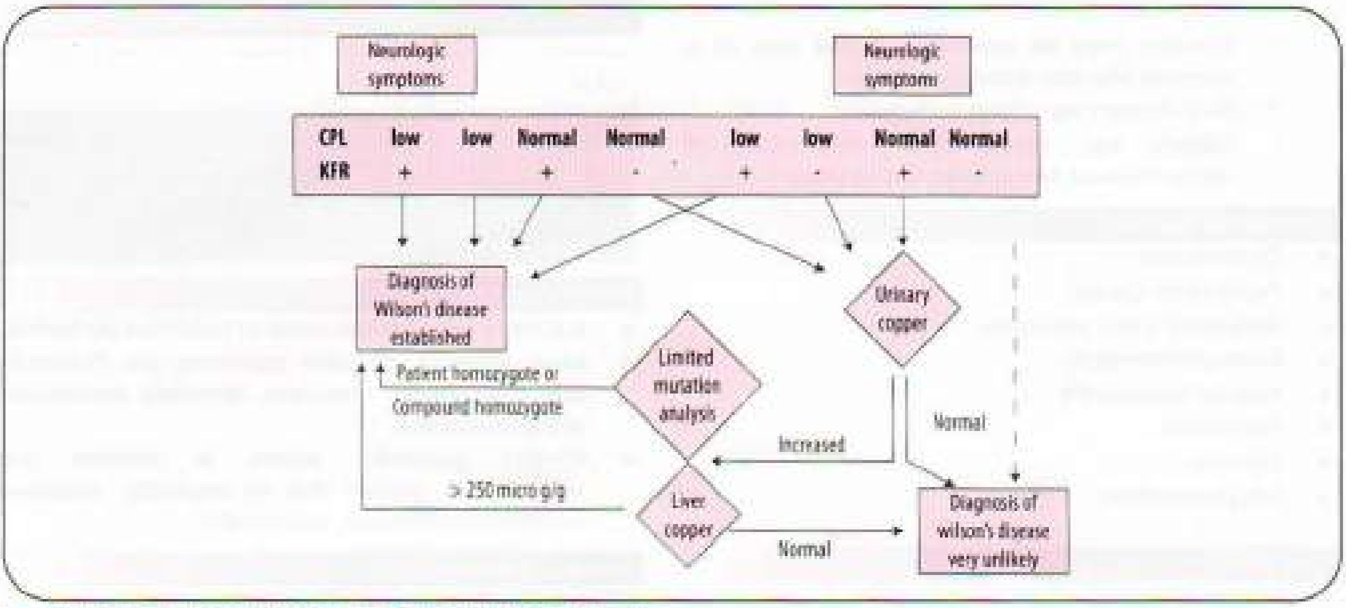

Neurologic symptoms
Neurologic symptoms
CPL low low Normal Normal low low Normal Normal
KFR + + - + - + -
Diagnosis of Wilson's disease established
Urinary copper
Limited mutation analysis
Patient homozygote or Compound homozygote
Normal
Increased
> 250 micro g/g
Liver copper
Normal
Diagnosis of wilson's disease very unlikely

Figure 12.11 Stepwise approach to diagnosis Wilson's disease. CPL (Ceruloplasmin Level), KFR (KF ring)

CHOLECYSTITIS

CASE

Cholecystitis and cholelithiasis: A 12-year-old boy is a known case of sickle cell disease. He presents with the complaints of increasing ***jaundice, abdominal pain***, nausea, vomiting, and ***fever***. On examination, he has jaundice and pain of the right upper quadrant with guarding. Chest radiograph is normal. Cholelithiasis is confirmed with an ultrasound of the gallbladder.

- Acute acalculous cholecystitis is usually caused by infection.
- Common pathogens include streptococci (groups A and B), Gram-negative organisms, e.g. *Salmonella*.
- Parasitic infestation may occur with *Ascarisor Giardia lamblia*.
- Calculous cholecystitis may occur following an abdominal trauma or burn injury.

Clinical findings

- Clinical findings include right upper quadrant or epigastric pain, nausea, vomiting, fever, and jaundice.
- Right upper quadrant guarding and tenderness are present.

Diagnosis

- Ultrasonography shows an enlarged, thick-walled gallbladder, with or without calculi.
- Serum alkaline phosphatase and direct-reacting bilirubin levels are raised.
- Leukocytosis is common.

Management

- Treatment of systemic and biliary infection is curative.
- Gallbladder may become gangrenous, so daily ultrasonography is helpful in monitoring gallbladder distention and wall thickness.
- Cholecystectomy is required in patients who fail to improve with above treatment.

ACUTE PANCREATITIS

CASE

An 11-year-old child presents with fever, nausea and vomiting for 5 days. She has epigastric pain which is radiating to the back. There is hyperglycemia and serum amylase is raised.

- Most cases of acute pancreatitis are the result of drugs, viral infections, systemic diseases, abdominal trauma, or obstruction of pancreatic flow.
- More than 20% cases are idiopathic.

Pathogenesis

- Inflammation of the pancreas is thought to result from the inappropriate intrapancreatic activation of pancreatic proteolytic enzymes.
- Activation of these enzymes leads to coagulation necrosis of the pancreas and can progress to retroperitoneal hemorrhage or abscess formation.

Clinical findings

- Symptomsinclude nausea, vomiting, and epigastric pain that often radiates to the back and may be relieved by leaning forward.
- Physical examination findingsinclude:
  - ○ Epigastric tenderness
  - ○ Diminished bowel sounds

  - Fever
  - Jaundice (may be prominent in the case of a common bile duct stone)
  - Grey-Turner's sign (flank ecchymosis)
  - Cullen's sign (periumbilical ecchymosis), if retroperitoneal hemorrhage has occurred

Differential diagnoses

- Cholelithiasis
- Peptic ulcer disease
- Abdominal aortic aneurysm
- Acute gastroenteritis
- Atypical appendicitis
- Pneumonia
- Volvulus
- Intussusceptions

Diagnosis

- Leukocytosis
- Elevated serum amylase (more than three times normal)
- Serum lipase
- Immunoreactive trypsinogen may be elevated
- Hyperglycemia (serum glucose >300 mg/dl)
- Hypocalcemia
- Falling hematocrit
- Rising blood urea nitrogen
- Hypoxemia and acidosis
- Plain radiographic films of the abdomen show a localized ileus (sentinel loop)
- Ultrasonography shows decreased echodensity of the gland in comparison with the left lobe of the liver. Pseudocyst may be seen
- CT scanning detects pancreatic phlegmon, or abscess formation

Management

- Nasogastric suction (and antiemetics) are indicated if the patient is vomiting.
- Acid suppression may be helpful.
- Careful attention is given to fluids, electrolytes, and respiratory status.
- Intravenous fluid hydration should be initiated, and a Foley catheter placed to monitor fluid status.
- Analgesics (opioids) may be necessary.
- Antibiotics should be administered only if there is evidence of infection.
- Drugs known to cause acute pancreatitis should be discontinued.
- Surgical treatment is needed for traumatic disruption of the gland, intraductal stone, other anatomic obstructive lesions, and infected pseudocysts or abscesses.

ACUTE PERITONITIS

CASE

A 9 years child with nephrotic syndrome presents with fever and vomiting, his abdomen is tender, rigid, and distended. There is involuntary guarding. Bowel sounds are absent.

Primary bacterial peritonitis

- It is much less common cause of childhood peritonitis.
- Most common causative organisms are *Escherichia coli*, other enteric organisms, hemolytic streptococci, and pneumococci.
- Primary peritonitis occurs in children with splenectomy, ascites due to nephrotic syndrome, advanced liver disease, kwashiorkor.

Secondary peritonitis

- It is a common cause of peritonitis in children.
- It is secondary to peritoneal dialysis, penetrating abdominal trauma, or ruptured viscus.

Clinical findings

- Symptoms of peritonitis include abdominal pain, fever, nausea, vomiting, acidosis, and shock.
- There is shallow respiration.
- Abdomen is tender, rigid, and distended. There is involuntary guarding.
- Bowel sounds may be absent.
- Diarrhea is common.

Diagnosis

- Leukocyte count may be high (>20,000/µL) with a predominance of immature forms.
- Plain abdominal radiographs and CT scan will confirm the presence of ascites.
- Bacterial peritonitis should be suspected if peritoneal fluid contains:
  - More than 500 leukocytes/µL
  - More than 32 mg/dL of lactate
  - If it has a pH less than 7.34
  - If the pH is over 0.1 pH unit less than arterial blood pH
- Diagnosis is made by Gram stain and culture. The blood culture is commonly positive in primary peritonitis.

Management

- Antibiotic treatment
- Supportive therapy for dehydration, shock, and acidosis is indicated
- Surgical treatment of the underlying cause of secondary peritonitis is curative
- Immediate removal of infected peritoneal dialysis catheters is indicated

Table 12.9: Difference between prebiotics and probiotics.

Prebiotics	Probiotics
These are natural energy source for healthy bacteria. That are present in intestine.	These are specific, live or dormant strains of healthy bacteria.
These are naturally present in breast milk.	These are not found in breast milk.
Their effect on healthy bacteria mimics effect of breast milk.	Their effect on healthy bacteria is less than with breast milk or prebiotics.
They have proven effect to naturally strengthen the immune system.	These are used to balance the intestinal flora that has undergone alterations with antibiotics use.
They have positive influence on entire gut microbiota.	They do not have positive influence on entire gut microbiota.

Notes

CHAPTER 13

Cardiovascular Disorders

FETAL AND NEONATAL CIRCULATION

Normal physiology

- Fetal blood is oxygenated in the placenta and then enters the umbilical vein.
    - One portion of the oxygenated blood enters the liver and then drains into inferior vena cava (via the hepatic veins).
    - Another portion enters the ductusvenosus and enters directly into the inferior vena cava.
- Together with venous return from the lower part of the body, the above mentioned blood flows into the right atrium.
    - In the right atrium, one third blood is shunted via foramen ovale to the left atrium, left ventricle, and ascending aorta.
    - The remainder of the blood in the right atrium joins venous return from the upper part of the body and enters the right ventricle and pulmonary artery. A small portion of this blood enters the lungs. The remainder, crosses the ductusarteriosus to the descending aorta.

Transition to neonatal circulation

- At birth, the infant's first breath causes an increase in arterial oxygen tension (PO_2) and lowers pulmonary vascular resistance, resulting in increased pulmonary blood flow. The increased pulmonary venous return to the left atrium causes the pressure to rise, which results in functional closure of the foramen ovale.
- Systemic vascular resistance is increased by the elimination of the low-resistance vascular circuit of the placenta at birth.
- Closure of the ductusarteriosus occurs shortly after birth:
    - Functionally as a result of a rise in PO_2 and a decrease in circulating prostaglandin E.
    - Anatomically as a result of fibrosis.
- The neonatal circulation is thus established. The ventricles work in series now.

CONGENITAL HEART DISEASE

- The cause of congenital heart disease is usually unknown but (in individual cases) evidence points to a multifactorial etiology, with the insult probably occurring in the first 8 weeks of gestation.
- Congenital heart disease has been associated with several teratogenic factors, e.g.
    - Maternal medications (folic acid antagonists, anti-convulsants, estrogens)
    - Maternal infections (rubella, cytomegalo-viruses)
    - Maternal diabetes mellitus
- Congenital heart disease may be a component of several syndromes, e.g.
    - Down syndrome
    - Turner syndrome
    - Marfan syndrome

Evaluation of congenital heart disease

- Congenital cardiac defects can be divided into 2 major groups based on the presence or absence of cyanosis (on physical examination or pulse oximetry).
- Acyanotic congenital heart disease
- Cyanotic congenital heart disease
- Further evaluation depends on whether the chest radiograph shows evidence of increased, normal, or decreased pulmonary vascular markings.
- Electrocardiogram can be used to determine whether right, left, or biventricular hypertrophy exists.
- The character of the heart sounds and the presence and character of any murmurs further narrow the differential diagnosis.
- The final diagnosis is then confirmed by echocardiography, CT or MRI, or cardiac catheterization.

Acyanotic heart diseases

Acyanotic lesions resulting in increased volume load:

- Ventricular Septal Defect (VSD).
- Patent DuctusArteriosis (PDA).
- Atrial Septal Defect (ASD).

Acyanotic lesions resulting in increased pressure load (obstruction to ventricular outflow:

- Valvular pulmonic stenosis
- Valvular aortic stenosis
- Coarctation of the aorta

Cyanotic heart diseases

Cyanotic lesions with decreased pulmonary blood flow:

- Tetralogy of Fallot (TOF)
- Tricuspid or pulmonary atresia

Cyanotic lesions with increased pulmonary blood flow:

- Transposition of the Great Arteries (TGA)
- Total anomalous pulmonary venous return
- Truncusarteriosus

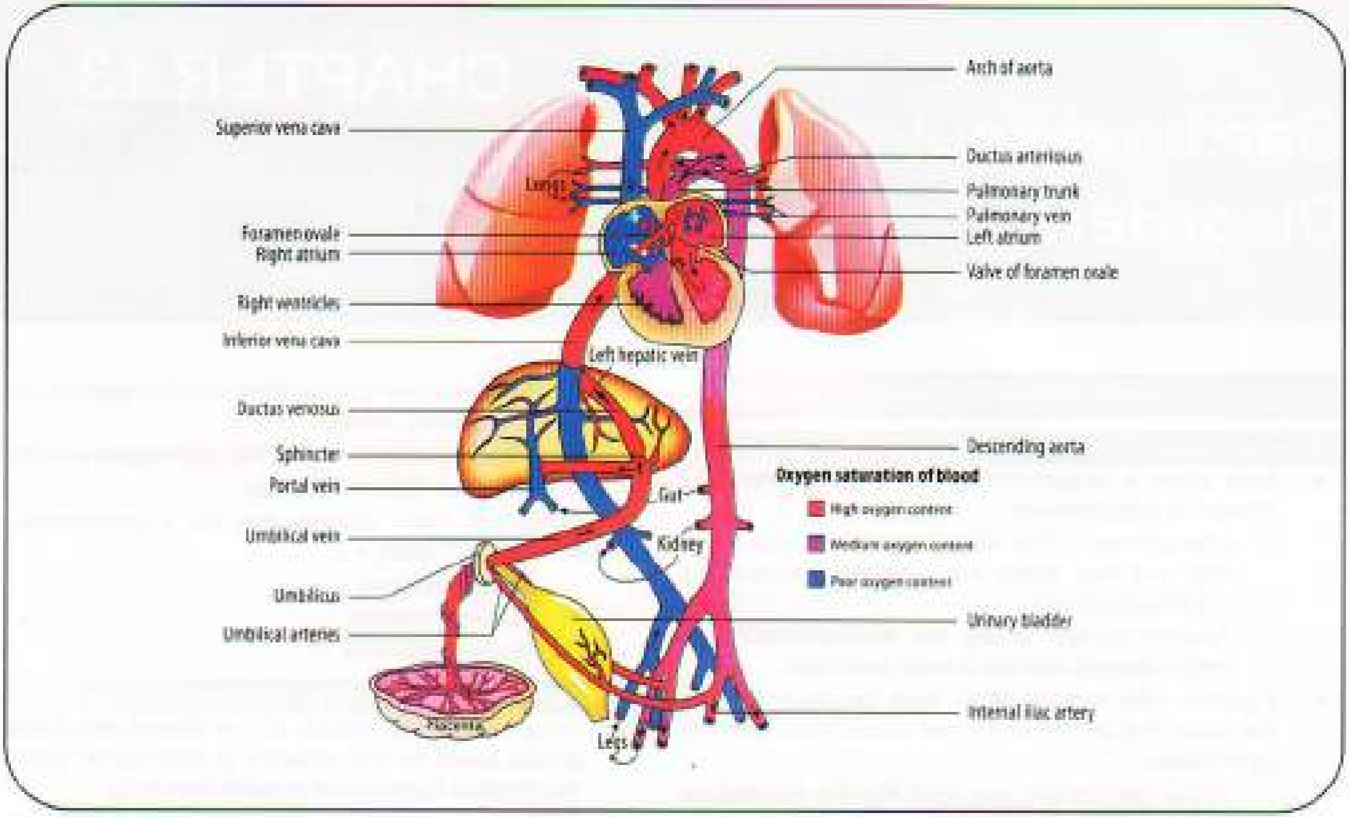

Arch of aorta
Superior vena cava
Ductus arteriosus
Lungs
Pulmonary trunk
Pulmonary vein
Foramen ovale
Left atrium
Right atrium
Valve of foramen ovale
Right ventricles
Inferior vena cava
Left hepatic vein
Ductus venosus
Sphincter
Descending aorta
Oxygen saturation of blood
Portal vein
Gut
🟥 High oxygen content
Umbilical vein
Kidney
▨ Medium oxygen content
🟦 Poor oxygen content
Umbilicus
Umbilical arteries
Urinary bladder
Placenta
Internal iliac artery
Legs

Figure 13.1: Fetal heart

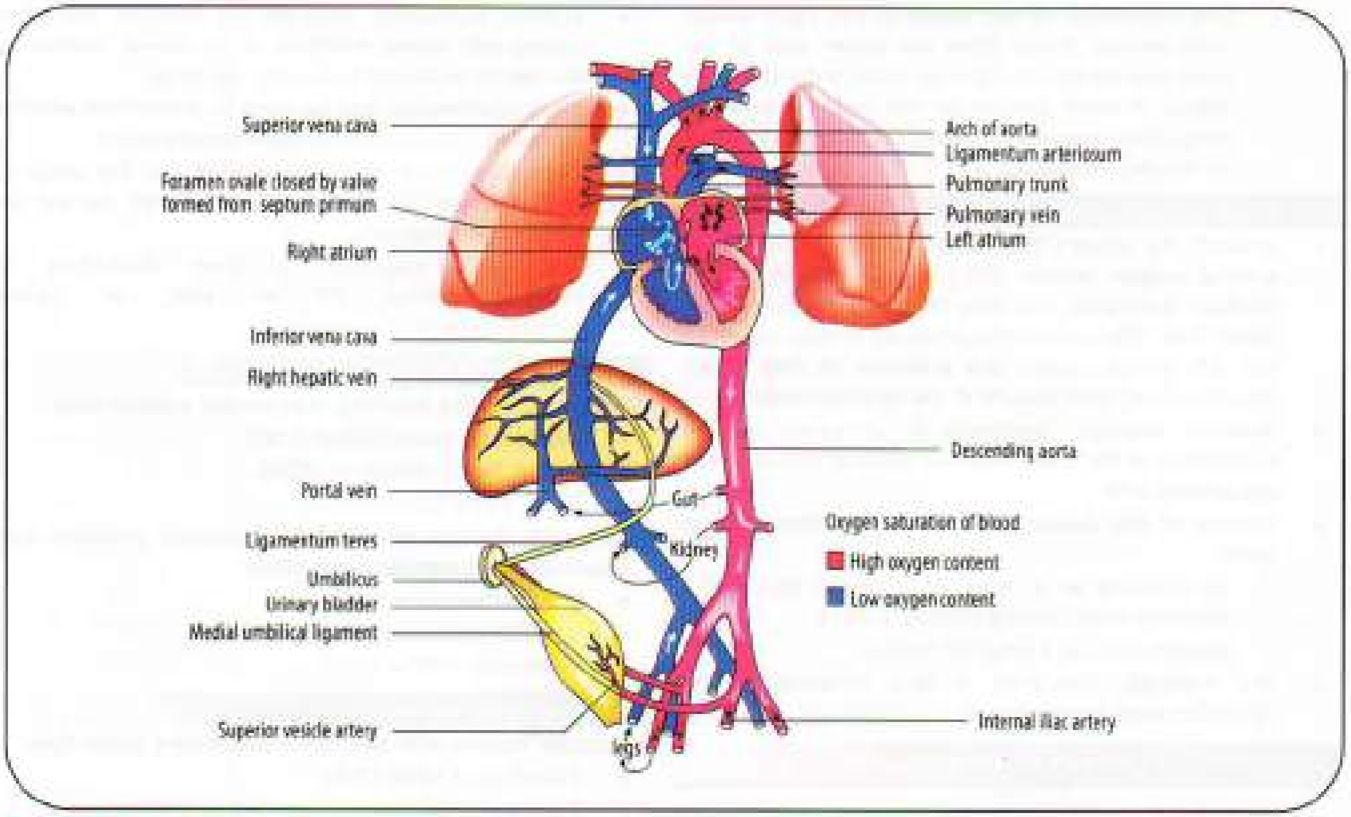

Superior vena cava
Arch of aorta
Ligamentum arteriosum
Foramen ovale closed by valve formed from septum primum
Pulmonary trunk
Pulmonary vein
Left atrium
Right atrium
Inferior vena cava
Right hepatic vein
Descending aorta
Portal vein
Gut
Oxygen saturation of blood
Ligamentum teres
Kidney
🟥 High oxygen content
🟦 Low oxygen content
Umbilicus
Urinary bladder
Medial umbilical ligament
Superior vesicle artery
Internal iliac artery
legs

Figure 13.2: Neonatal heart

Incidence

- Congenital heart disease affects 8: 1000 births.
- 30% of infants with heart lesions also have extracardiac malformations.

Relative frequency of major congenital heart lesions

- Ventricular septal defect (25–30%)
- Atrial septal defect (secundum)(6–8%)
- Patent ductusarteriosus (6–8%)
- Coarctation of aorta (5–7%)
- Tetralogy of Fallot (5–7%)
- Pulmonary valve stenosis (5–7%)
- Aortic valve stenosis (4–7%)
- D-Transposition of great arteries (3–5%)
- Hypoplastic left ventricle (1–3%)
- Truncusarteriosus (1–2%)
- Total anomalous pulmonary venous return (1–2%)
- Tricuspid atresia (1–2%)

CYANOTIC HEART DISEASE

TETRALOGY OF FALLOT (TOF)

CASE

A 2-year-old child presents with failure to thrive, cyanosis and clubbing. X-ray chest shows the normal heart size, some elevation of the cardiac apex, concavity in the region of the main pulmonary artery (***boot shaped heart***), right-sided aortic arch and ***diminished pulmonary vascularity***. ECG shows right axis deviation (RVH). Echocardiography demonstrates all the four components of TOF. ABGs show metabolic acidosis.

- This is the most common cyanotic congenital heart lesion (5–7%), which is compatible with life.

Components

TOF comprises of following defects:

1. Pulmonary stenosis.
2. Ventricular Septal Defect (VSD).
3. Overriding of the aorta (over the ventricular septum).
4. Right ventricular hypertrophy.
5. An Atrial Septal Defect (ASD) is present in 15% of cases and right aortic arch is present in 25% of cases.

Pathophysiology

- The VSD and pulmonary stenosis are physiologically the most important components.
- The degree of pulmonary stenosis determines the right-to-left shunt and cyanosis.
- Pulmonary stenosis is mainly infundibular (50–70%), but also involves the valve.
- Right ventricular hypertrophy is secondary to right ventricular outflow obstruction.
- Right-to-left shunt also depends on the size of VSD and systemic vascular resistance (blood pressure).
- Persistent arterial de-saturation results in cyanosis.

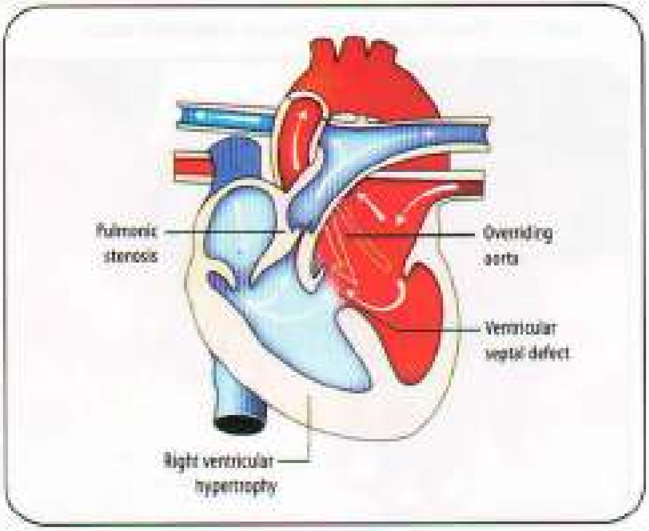


Figure 13.3: Tetralogy of Fallot (TOF).

Clinical findings

- The degree of right ventricular outflow obstruction determines the timing of onset of symptoms. Baby may not be cyanosed at birth. The right ventricular outflow tract obstruction is progressive, resulting in increasing hypoxemia and cyanosis over the first few months and years of life.
- Growth and development are retarded.
- There is digital clubbing and dyspnea at rest. Dyspnea occurs on exertion. Infants and toddlers will play actively for a short time and then sit or lie down. Characteristically, children assume a squatting position as it decreases systemic venous return and increases systemic vascular resistance thereby decreasing right-to-left shunt.
- Paroxysmal hypercyanotic attacks (hypoxic, blue or tet spells) are a particular problem during the first 2 years of life. The infant becomes hyperpneic and restless, cyanosis increases, gasping respiration occurs, and syncope may follow. The spells occur most frequently in the morning upon awakening or following episodes of vigorous crying. During a spell, there is a decrease in intensity or disappearance of the systolic murmur as flow across the right ventricular outflow tract diminishes.
- The pulse is usually normal.
- The left anterior hemithorax may bulge anteriorly due to right ventricular hypertrophy.
- The heart is usually normal in size, and there is a left parasternal heave.
- In 50% of cases, a systolic thrill is felt along the left sternal border in the 3rd and 4th parasternal spaces.
- Second heart sound (S2) is often single, or the pulmonic component is soft. A harsh ejection systolic murmur is heard along the left sternal border in the 3rd intercostal space; its length and loudness are inversely proportional to the degree of outflow obstruction. No

murmur is audible from a right-to-left shunt through VSD. The volume work of the heart in TOF is less than normal; therefore, heart failure does not occur.

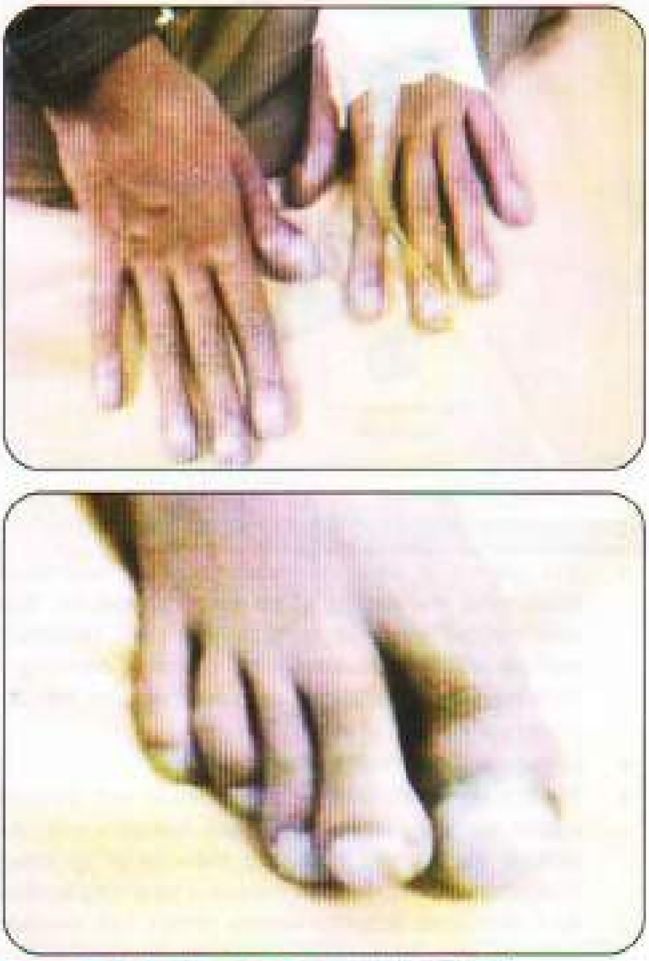


Figure 13.4: Clubbing in a 7 years child with TOF.

Diagnosis

Blood Counts

- The hemoglobin, hematocrit, and RBCs count are usually mildly to markedly elevated, depending on the degree of arterial oxygen saturation.

Chest X-ray

- The heart size is normal. The apex is lifted and a concavity is noted in the pulmonary segment, giving the heart the appearance of a boot (boot shape heart).
- The pulmonary vascular markings are diminished (oligemic lung fields).
- The aortic arch is right-sided in 25% of cases.

ECG

- It shows right axis deviation and right ventricular hypertrophy.

Echocardiography

- Right ventricular hypertrophy, pulmonary stenosis, ventricular septal defect and overriding of aorta can be demonstrated.

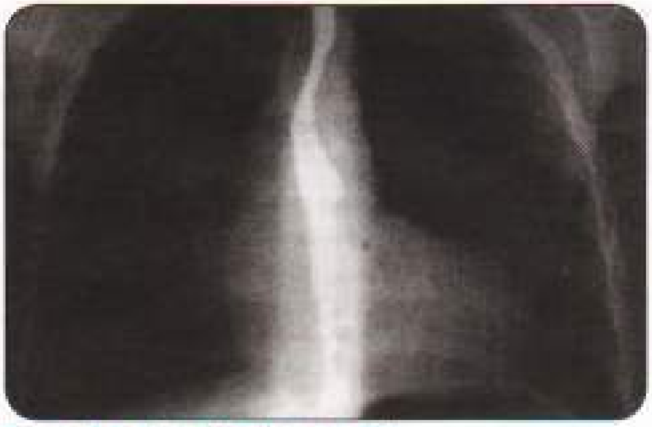


Figure 13.5: Boot shape heart in TOF.

Cardiac catheterization and angiography

- It is to clarity pulmonary artery and coronary artery anatomy.

Complications

- **Cerebrovascular Accident** (CVA) or **cerebral thromboses** : In children younger than 2 years of age, this complication almost invariably is secondary to hypoxemia and anemia rather than polycythemia, sludging, and in situ thrombosis.
- Brain abscess: It presents with fever, headache, vomiting, and cranial nerve palsies with raised intracranial pressure or other localizing signs. Mainly seen in children more than 2 years of age. It is due to right-to-left shunting.
- Bacterial endocarditis is due to strep viridans.
- Polycythemia is due to persistent hypoxia.
- Relative anemia is due to nutritional deficiency.
- Failure to thrive is due to increased oxygen consumption and decreased nutritional intake.
- Psychosocial problems due to chronic disease and multiple hospitalizations.

Management

- The aim of therapy is to increase the pulmonary blood flow and prevent hypoxemia.

- Maintain adequate hydration to avoid hemoconcentration and possible thrombotic episodes.
- Temperature maintenance to limit oxygen consumption.
- Blood glucose levels should be monitored to prevent hypoglycemia.
- Hemoglobin and hematocrit should be maintained within normal range.
- Give iron supplements to improve exercise tolerance.
- Bacterial endocarditis prophylaxis is necessary. Oral hygiene must be maintained.
- Partial exchange transfusion or phlebotomy for polycythemia may be required.
- Antibiotic and drainage for brain abscess.

- To prevent growth retardation, correct defect early and increase caloric intake.
- Counseling is necessary for psychosocial problems.

Management of hypoxemic spells

- Oxygen inhalation.
- Place the child in a knee-chest position to increase systemic vascular resistance and diminish right-to-left shunting.
- Morphine sulfate (0.2 mg/kg subcutaneously) is given to decrease anxiety and to prevent sympathetic overdrive.
- To correct acidosis, intravenous sodium bicarbonate may be given.
- β-receptor blocking agent (e.g. propranolol in a dose of 0.1–0.2 mg/kg slow intravenous) is given to decrease the muscular spasm of the infundibulum. Cyanotic spells can be prevented by propranolol (1 mg/kg orally every 6 hours) until total correction is done.

Surgical management

Palliative surgery

- A temporary increase in pulmonary blood flow can be obtained by the creation of a systemic artery-to-pulmonary artery shunt.
  - **Blalock–Taussig shunt:** In this, right subclavian to pulmonary artery anastomosis is done.

Corrective surgery

- It consists of closing the VSD and resecting the right ventricular outflow obstruction, and, if necessary, enlarging the area with a patch.
- The timing of total correction ranges from 3 months to 2 years depending upon the expertise available.
- Complications of corrective surgery are conduction disturbances like right bundle branch block or premature ventricular beats.

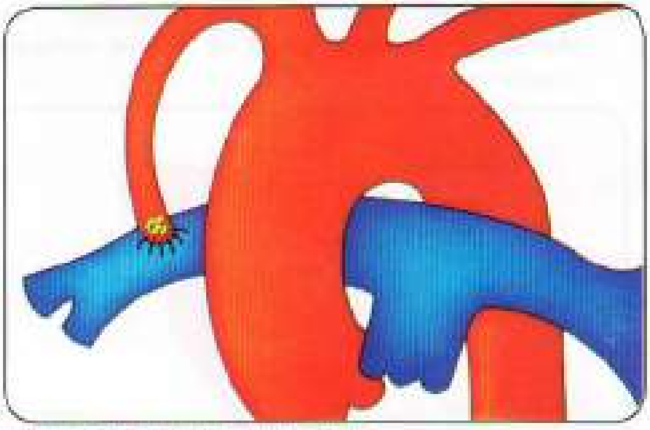


Figure 13.6: Blalock-Taussig shunt.

Course and prognosis

- Infants with the most severe form of the disease are usually deeply cyanotic at birth. Hypoxemic spells may occur during the neonatal period. Death may occur during a severe hypoxemic spell.
- Many patients who survive the first year of life seem to improve. This may be because of the development of systemic-to-pulmonary collateral vessels. Hypoxemic spells may decrease in severity but they seldom survive the second decade of life without surgical treatment.
- Complete repair prior to the school age have good survival, but sudden death may occur from dysrhythmias.

TRANSPOSITION OF GREAT ARTERIES (TGA)

CASE

A 3-day-old infant presents with ***progressively deepening cyanosis*** since birth but ***no respiratory distress.*** He is well at birth but at 6 hours of age cyanosis started. Oxygen saturation is 80%. Chest radiograph shows no cardiomegaly and normal pulmonary vasculature. An electrocardiogram shows an axis of 120° and right ventricular prominence.

- This is the most serious cyanotic lesion seen in newborn period (5%), and they rarely survive.
- In TGA, the aorta arises from the right ventricle and pulmonary artery arises from the left ventricle.
- Associated abnormalities may include VSD, PDA, pulmonary stenosis, or a combination of these.
- TGA is more common in infants of diabetic mothers and in males (3:1).

Pathophysiology

- Desaturated blood reaching from the body to the right side of the heart passes through the aorta and back to the systemic circulation again.
- Oxygenated pulmonary venous blood returning to the left side of the heart is returned directly to the lungs through pulmonary artery.
- *Thus, the systemic and pulmonary circulation consists* of two parallel circuits.
- The only means of survival in these newborns is mixing of oxygenated and deoxygenated blood by persistence of patent foramen ovale, ductusarteriosus, or VSD.

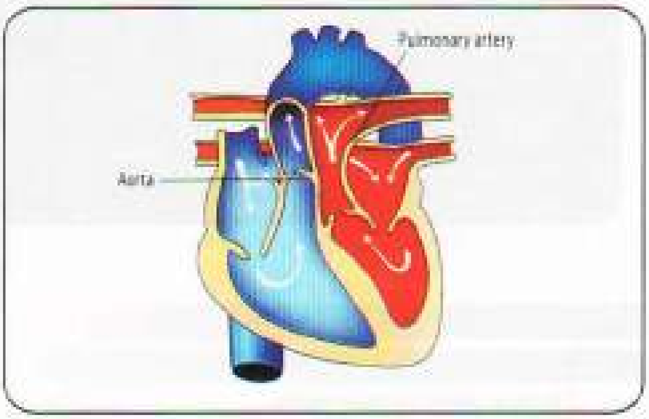


Figure 13.7: TGA: Aorta arises from the right ventricle and pulmonary artery arises from the left ventricle.

- Congestive heart failure may develop with VSD because of the high cardiac output.

Clinical findings

- These vary and depend upon the associated VSD, foramen ovale or PDA.

TGA with intact ventricular septum

- In TGA with intact ventricular septum, prior to birth, oxygenation of the fetus is nearly normal; but after birth, once the ductus begins to close, the minimal mixing of the systemic and pulmonary blood via the patent foramen ovale is insufficient and severe hypoxemia occurs.
- Cyanosis and tachypnea are most often recognized within the first few hours or days of life.
- Untreated, the vast majority of these infants would not survive the neonatal period.
- Hypoxemia is usually severe; congestive heart failure is less common.
- It is a medical emergency, and needs early diagnosis and appropriate management.

TGA with ventricular septal defect (VSD)

- In TGA with VSD, significant mixing of (oxygenated and deoxygenated) blood occurs and congestive cardiac failure is common.
- Mild cyanosis may be recognized within the 1st month of life.
- The murmur is short systolic and P_2 is loud and generally indistinguishable from that produced by a large VSD.
- Many of the neonates are large, some weighing 4 kg at birth.
- Retardation of growth and development after the neonatal period is common.

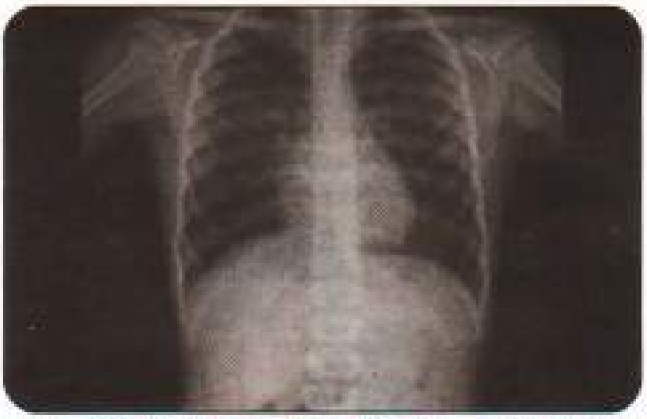


Figure 13.8: Heart shape looks like an egg placed on its side.

Diagnosis

Chest X-ray

- There is slight cardiomegaly.
- A narrow base produced by the anterior-posterior arrangement of the great arteries give the appearance of a narrow pedicle and heart shape looks like **an egg placed on its side.**
- Pulmonary vascularity may be increased or normal.

ECG

- ECG shows the normal neonatal right-sided dominant pattern.
- Afterwards, the ECG shows combined ventricular hypertrophy or occasionally pure right ventricular hypertrophy.

Echocardiography

- It shows the anterior-posterior arrangement of the great arteries, and origin of the aorta from the right ventricle and pulmonary artery from the left ventricle.

Arterial blood gases

- There is severe hypoxemia and arterial PO_2 does not rise after administration of 100% oxygen (hyperoxia test).

Management

- The survival of patients with TGA depends on early, aggressive management.

Medical management

- Prostaglandin (PGE_1) infusion is started immediately (in a dose of 0.05–0.20 µg/kg/minute) to maintain the patency of the ductusarteriosus.
- Hypothermia should be corrected as it intensifies the metabolic acidosis from hypoxemia.
- Prompt correction of acidosis and hypoglycemia is essential.
- In infants with heart failure, the usual anti-congestive measures, including digoxin, diuretics, increased caloric density of the formula, and afterload reduction are helpful.

Surgical management

- All patients with favorable anatomic and hemodynamic criteria should be offered corrective surgery by the age of 2 weeks.

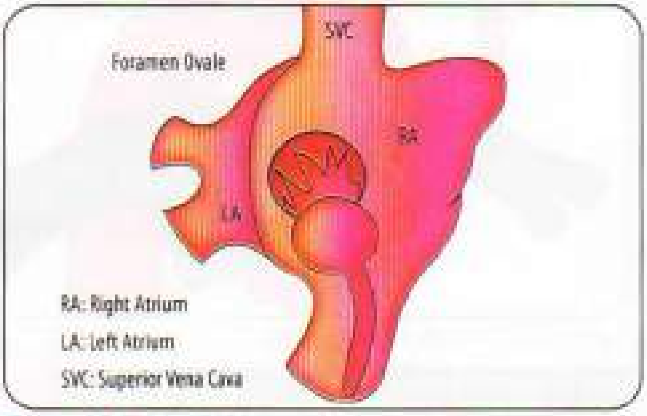


Figure 13.9 : Rashkind procedure

- **Rashkind procedure** or **balloon atrial septostomy** is the initial palliation performed by rupturing atrial septum through the fossa ovalis with a balloon catheter.

- **Mustard procedure** involves insertion of an intra-atrial baffle, which redirects systemic and pulmonary venous blood to the aorta and pulmonary artery respectively.
- **Total repair** by an **arterial switch technique** is the surgical treatment of choice for neonates having TGA with intact ventricular septum.

Prognosis

- When a TGA is left untreated, the prognosis is poor, with 30% of affected infants dying in the 1st week of life, 50% in the first month, and more than 90% in the 1st year of life because of hypoxia, congestive heart failure and pulmonary hypertension.
- The arterial switch procedure has a survival rate of 90–95% for uncomplicated TGA.

EBSTEIN ANOMALY

CASE

A 2-year-old child presents with minimal ***cyanosis***. On clinical examination, he has an S3 and S4 (***a quadruple rhythm***), a ***systolic murmur*** in the pulmonic area, a ***mid-diastolic murmur*** along the lower left sternal border. An electrocardiogram shows right atrial hypertrophy and a ventricular block (right bundle branch block) pattern in the right chest leads (superior axis). X-ray chest showing massive cardiomegaly, ***box shaped heart*** (wall to wall heart), reduced pulmonary vasculature.

- The tricuspid valve is malformed.
- There is downward displacement of the tricuspid valve into the body of the right ventricle.
- Tricuspid valve is frequently regurgitant, resulting in marked right atrial enlargement and a large right-to-left shunt at the atrial level.
- There is little right ventricular outflow into the pulmonary circulation.
- The pulmonary blood flow is severely limited with profound hypoxemia and acidosis.

Clinical findings

- Cyanosed at birth
- Loud murmur of tricuspid regurgitation
- Can be very sick
- May be associated with maternal lithium ingestion

Associations

- Ebstein anomaly is often associated with:
  - Wolff Parkinson White (WPW) syndrome.
  - Supraventricular Tachycardia (SVT).

Diagnosis

- ECG:
  - Right axis and right bundle branch block.
- CXR:
  - Massive cardiomegaly (wall to wall heart).
  - Reduced pulmonary vascular markings.

Management

- Resuscitate.
- Prostaglangin E (PGE) is used to maintain a patent ductusarteriosus.
- Other measures to decrease pulmonary vascular resistance (Pulmonary vasodilator therapy) are
  - Ventilation
  - Oxygen
  - Maintaining a mild respiratory alkalosis

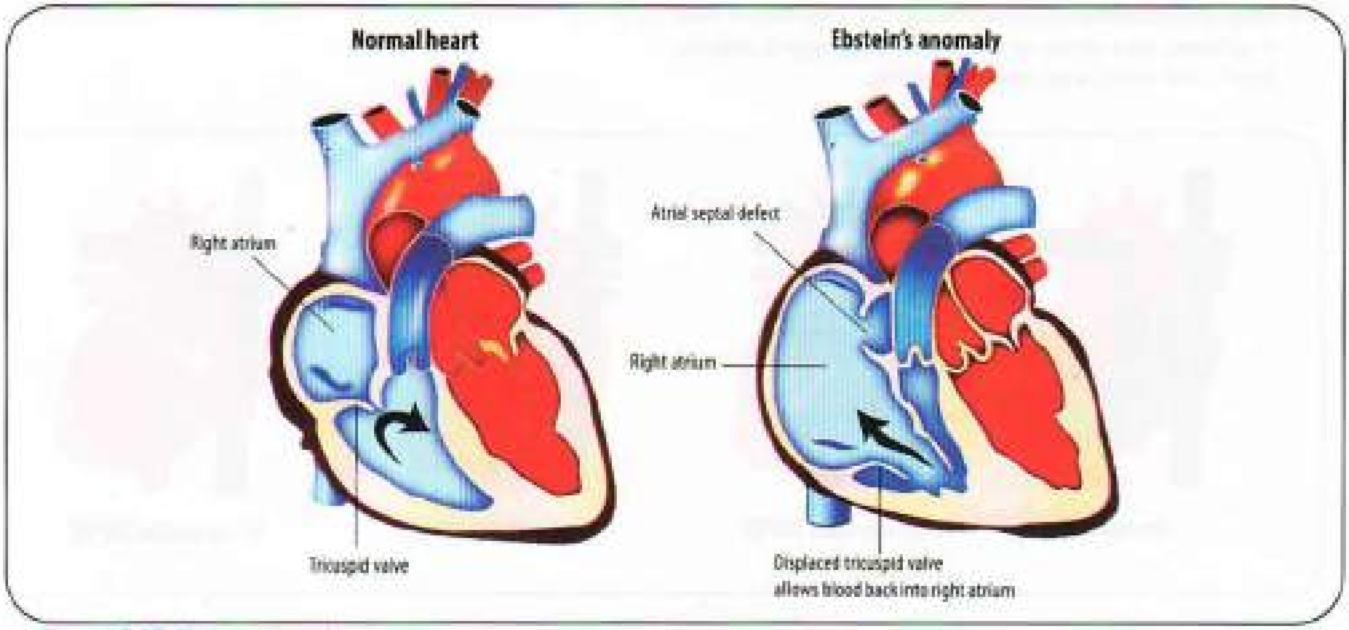


Figure 13.10: Ebstein anomaly

- Nitric oxide is used with limited success.
- Try to avoid surgical shunt insertion, in which case prognosis is poor.
- An important contributor to the high mortality rate with severe Ebstein anomaly is the associated pulmonary hypoplasia due to massive enlargement of heart in utero.
- In newborns, consider closure of tricuspid valve and aortopulmonary shunt, or transplantation.
- In older children, tricuspid valve repair or valve replacement and ASD closure.

TOTAL ANOMALOUS PULMONARY VENOUS RETURN OR CONNECTION (TAPVC)

CASE

A 3-month-old infant presents with severe ***dyspnea*** and ***cyanosis***. Chest X-ray shows minimal cardiomegaly figure 8 that appearance like.

- All of the pulmonary veins fail to connect to the left atrium and return abnormally via the right side of the heart.
- They may have **supracardiac**, **infracardiac**, **cardiac**, or **mixed drainage**.
- An atrial-level communication is required for systemic cardiac output and survival.

Clinical findings

- With **unobstructed pulmonary venous drainage to the right atrium**, there is:
  - High pulmonary blood flow
  - Cardiomegaly
  - Congestive heart failure
  - Mild cyanosis
- With **obstructed pulmonary return** (venous return into a systemic vein above or below the diaphragm), infants have small heart with severe cyanosis.
- There is a hyperactive right ventricular impulse with a widely split S2 (owing to increased right ventricular volume) and a systolic ejection murmur at the left upper sternal border.
- Growth is relatively poor.

Diagnosis

- Cardiomegaly with increased pulmonary blood flow is seen on chest X-ray. There is dilation of both the left and right innominate veins and the right superior vena cava producing the classical "snowman" or "figure of 8" appearance.
- ECG shows right atrial and right ventricular hypertrophy.
- Echocardiography with color flow doppler can suggest this anomaly but definitive diagnosis may still require cardiac catheterization.

Differential diagnosis

- Other cyanotic congenital heart disease
- Persistent fetal circulation

Management

- Immediate surgery required if pulmonary venous return is obstructed.
- In unobstructed patients surgery may be delayed for weeks to months.
- At **surgery**, the common pulmonary vein is opened into the left atrium, and there is ligation of any vein or channel that had been draining the common vein.
- **Balloon atrial septostomy** may be a palliative maneuver to improve mixing at the atrial level.
- Surgical outcome is very good.
- 5% develop late stenosis of the pulmonary veins, which has a poor prognosis.

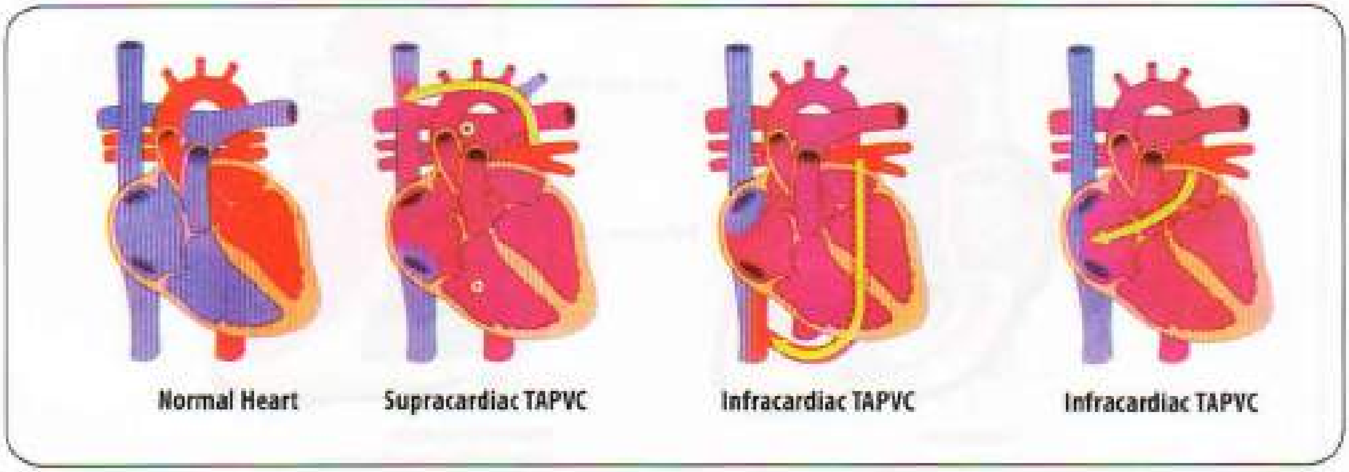


Figure 13.11: Different types of TAPVC

TRUNCUS ARTERIOSUS

CASE

A 20 days old boy presents with ***respiratory distress*** and ***mild central cyanosis***. Respiratory rate is 70/minute, pulse rate 147/minute and BP 80/35 mmHg. Pulse is bounding, pericardium active with ***a single loud P2***, and grade 3/6 ejection systolic murmur heard best at apex and left sternal border. A chest X-ray shows cardiomegaly with increased vascular markings. ECG shows normal sinus rhythm with right QRS axis deviation and ***biventricular hypertrophy***.

- It results from the failure of septation of the truncus during the first 3 to 4 weeks of gestation.
- A **single arterial trunk** arises from the heart with a large VSD immediately below the truncal valve.
- The pulmonary arteries arise from the single arterial trunk either as a single vessel that divides or individually from the arterial trunk to the lungs.

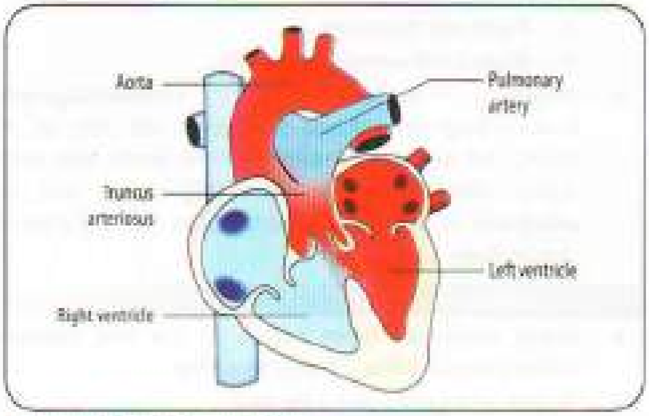


Figure 13.12: Truncus arteriosus.

Clinical findings

- Early congestive heart failure. (If not diagnosed at birth, the infant may develop signs of heart failure as pulmonary vascular resistance decreases. The signs then include tachypnea and cough).
- Mild or no cyanosis.
- A single **S2** is due to the single valve. There may be a systolic ejection click, and there is often a **systolic murmur** at the left sternal border.
- Symptoms depend on magnitude of pulmonary flow, which depends on truncal valve function and the size of the pulmonary arteries.
- High pulmonary flow is most common—presents like a VSD with congestive failure.
- Low pulmonary flow patients do poorly with cyanosis, poor growth, fatigue, dyspnea, and congestive failure.

Diagnosis

- **ECG** findings include combined ventricular hypertrophy and cardiomegaly.
- A **chest X-ray** usually reveals increased pulmonary blood and may show displaced pulmonary arteries.
- **Echocardiography** shows the anatomy, including the VSD, truncal valve function, and origin of the pulmonary arteries.

Differential diagnosis

- High-flow truncusarteriosus may be mistaken for a large VSD based on symptoms.

Management

- **Anticongestive treatment** with diuretics for high pulmonary flow.
- Surgery for high-flow states should be performed before 6 months of age to avoid the development of pulmonary vascular obstructive disease.
- Surgery for high-flow state—closure of VSD, separation of pulmonary arteries from the truncus with conduit from RV to pulmonary arteries (often an allograft).
- Children almost always outgrow their original conduit and need revision in childhood.

TRICUSPID ATRESIA

CASE

A newborn presents with ***marked cyanosis*** at birth. On auscultation, there is ***single S2***. Chest X-ray shows a mildly enlarged cardiac shadow with decreased pulmonary blood flow. ECG shows left axis deviation, ***large right atrium*** and ***left ventricle hypertrophy***.

- The absence of the tricuspid valve results in a hypoplastic right ventricle.
- All systemic venous return must cross the atrial septum into the left atrium.
- A PDA or VSD is necessary for pulmonary blood flow and survival.

Clinical findings

- Marked cyanosis at birth
- Delayed growth and development
- Exhaustion with feedings
- **Single S2**
- VSD murmur may be present
- Frequently there is no significant murmur

Diagnosis

- The **chest X-ray** reveals a normal or mildly enlarged cardiac silhouette with decreased pulmonary blood flow.
- **ECG**
- Left axis deviation
- A superior QRS axis (between 0° and–90°)
- Large right atrium
- Left ventricle hypertrophy
- **Echocardiography** is diagnostic. Echocardiography shows the anatomy, associated lesions, and source of pulmonary blood flow.

Differential diagnosis

- Other cyanotic congenital heart disease.
- Lung disease.

Management

- If there is high pulmonary artery flow—anticongestive therapy with diuretics pulmonary banding to reduce pulmonary artery flow.
- If there is decreased pulmonary flow—PGE1 used to keep ductusarteriosus open until aortopulmonary shunt (Blalock-Taussig) restores pulmonary flow.
- Ultimately, all children require a bidirectional cavopulmonary shunt (bidirectional Glenn) and Fontan procedure (inferior and superior vena cava connected to pulmonary artery) to ensure pulmonary blood flow without a functioning right ventricle.
- Antibiotic prophylaxis for endocarditis required after surgical shunting or pulmonary banding.

Prognosis

- Prognosis after Fontan is best in those with low pulmonary artery pressure preoperatively.
- Outcome depends upon how well one achieves a balance between adequate and excessive pulmonary flows by medication, banding, or surgery.

HYPOPLASTIC LEFT HEART SYNDROME

CASE

A baby boy appears ***well at birth***. Now at one day of age, he is feeding poorly, and is noted unwell with ***cyanosis*** and ***breathlessness***. On examination, he has cyanosis. Respiratory rate is 60 per minute with breathlessness and heart rate is 180/minute. On palpation the ***liver edge is 2 cm*** below the costal margin. There is a subxiphoid heave. All ***pulses are difficult to palpate***. ***No murmur*** is heard. Saturation is 65 per cent. On ECG, there are ***absent left ventricular forces***.

- It is the most common cause of death from cardiac defects in the first month of life.
- Hypoplastic left heart syndrome occurs when there is failure of development of the mitral or aortic valve or the aortic arch.
- A small left ventricle that is unable to support normal systemic circulation is a central finding, regardless of etiology.
- Associated degrees of hypoplasia of the ascending aorta and aortic arch are present.
- Left-to-right shunting occurs at the atrial level.

Clinical findings

- The newborn is dependent on right-to-left shunting at the ductusarteriosus for systemic blood flow.
- As the ductusarteriosus closes, the infant becomes critically ill with signs and symptoms of heart failure from excessive pulmonary blood flow and obstruction of systemic blood flow.
- Pulses are diffusely weak or absent (absent femoral, brachial pulses).
- S2 is single and loud.
- Minimal auscultatory findings. There is usually no heart murmur.
- Cyanosis may be minimal.
- Low cardiac outputgives a grayishcolor to the cool, mottled skin.
- Signs of right heart failure (hepatomegaly, low cardiac output).
- Uniformly fatal without treatment.

Diagnosis

- Diagnosis is often made prenatally by ultrasonography at 18–20 weeks.
- **CXR**:
  - Normal or cardiomegaly with heart failure.
- **ECG**:
  - Right axis deviation
  - Absent left ventricular forces
- Diagnosis confirmed by **echocardiography**. Echocardiography shows the small left side of the heart, the degree of stenosis of the aortic and mitral valves, the hypoplastic ascending aorta, and the adequacy of left-to-right atrial flow and right-to-left ductal flow.

Differential diagnosis

- Other causes of heart failure in the first month—coarctation of aorta, cardiomyopathy
- Severe acute pulmonary disease
- Multi-organ failure from septicemia

Management

- Continuous IV prostaglandin E1 maintains patency of ductusarteriosus.
- Nitrogen added to inhaled air lowers inspired O_2 to <21%, increases pulmonary vascular tone, and improves systemic perfusion.
- Surgical palliation—Norwood operation uses the right ventricle as the systemic ventricle with an aortopulmonary shunt for pulmonary blood flow.
- Cardiac transplantation is a second surgical option.
- Prophylaxis for endocarditis required after the Norwood operation.

ACYANOTIC HEART DISEASE

VENTRICULAR SEPTAL DEFECT (VSD)

CASE

A 2-month-old baby girl was doing well but now she presents with poor feeding, sweating and respiratory distress. Examination shows a ***tachypneic infant*** with normal pulses, marked heave, and a ***soft holosystolic heart murmur*** at the ***lower left sternal edge***. Liver is palpable (***hepatomegaly***) and chest X-ray shows cardiomegaly (***cardiac failure***).

- This is the most common congenital cardiac defect and comprises 25% of all congenital heart lesions.
- Defect may be in membranous part of the ventricular septum (most common) or the muscular part of ventricular septum.
- The VSD may be small or restrictive (usually <0.5 cm^2), moderate (0.5–1.0 cm^2), or large or non-restrictive (usually >1.0 cm^2).

Pathophysiology

- There is a left-to-right shunt and it depends upon the size of defect and the ratio of systemic to pulmonary vascular resistance.
- Left-to-right shunt occurs after first few weeks of life as pulmonary vascular resistance falls.
- There is bi-ventricular hypertrophy. The right ventricle has to deal with increased blood volume (normal venous return + blood shunted from left ventricle). There is also left ventricular hypertrophy with dilatation due to increased pulmonary blood flow that contributes to pulmonary hypertension.
- When pulmonary hypertension occurs, pulmonary vascular resistance is increased than systemic vascular resistance, shunt becomes reverse, signs of heart failure diminish, and the patient becomes cyanotic (Eisenmenger physiology).

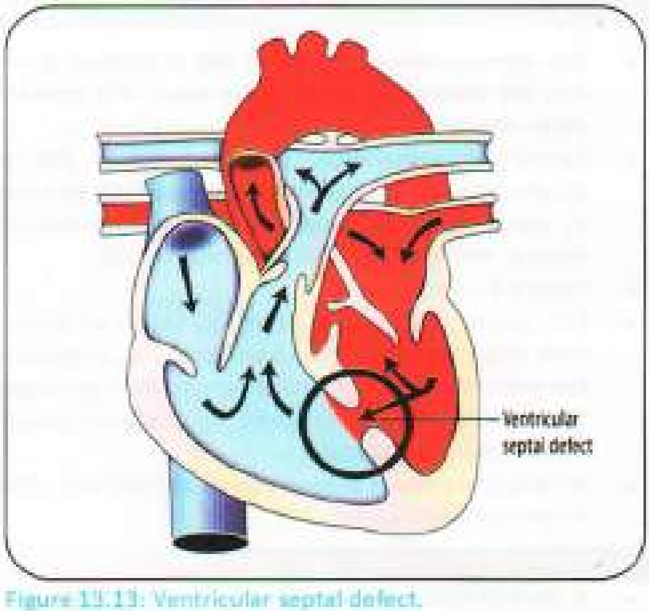


Figure 13.13: Ventricular septal defect.

Clinical findings

- The clinical presentation varies according to the size of the defect and the amount of pulmonary blood flow and pressure.

Small VSD

- In small VSD, the patients are asymptomatic and cardiac lesion is picked up on routine physical examination.
- Both heart sounds are normal and there is pansystolic murmur (loud and harsh) best heard at the lower left sternal border, and frequently accompanied by a thrill.
- The left-to-right shunt may be limited in the neonate because of higher right-sided pressures, and therefore the systolic murmur may not be audible during the first few days of life.

Moderate VSD

- In moderate VSD, there is moderate left-to-right shunt with increased pulmonary vascular resistance.
- During infancy, there is tachypnea, dyspnea, feeding difficulties, recurrent respiratory infections and growth retardation.
- Congestive cardiac failure may occur.
- There is a systolic thrill with normal 1st heart sound.
- Second heart sound is split with loud P_2.
- A loud pansystolic murmur will be heard at left sternal edge.

Large VSD

- In large VSD, there is excessive pulmonary blood flow and pulmonary hypertension is present.
- There is dyspnea, feeding difficulties, sweating, poor growth and recurrent pulmonary infections.
- Heart failure occurs from early infancy.
- Cyanosis may occur during crying.
- Sternum is bulging with apical thrust and systolic thrill at left sternal edge.
- There is loud P_2 and closely split 2nd heart sound.
- There is a pansystolic murmur (less harsh and more blowing) at left sternal edge. A mid-diastolic rumbling murmur may be heard at the apex from torrential blood flow across the mitral valve. The ejection systolic murmur may be heard at pulmonary area.

Diagnosis

Chest X-ray

- In small defects, the chest X-ray may be normal or show mild cardiomegaly and a slight increase in pulmonary vascularity.
- In large defects, there is cardiomegaly, increased pulmonary vascularity, and enlargement of the left atrium and left ventricle is seen. With pulmonary hypertension, distal pulmonary arteries become smaller but the proximal pulmonary arteries enlarge.

ECG

- In small defects, the ECG is normal.
- In large defects, biventricular hypertrophy is seen. P waves may be notched or peaked.
- Right ventricular hypertrophy predominates when pulmonary vascular resistance is high. An extreme left

axis deviation is characteristic of VSD in the endocardial cushion region (as in Down syndrome).

Echocardiography

- The two-dimensional echocardiogram will show the position and size of the VSD.

Cardiac catheterization

- It can demonstrate pressure and oxygen saturation in different chambers.

Management

Medical management

- In patients with small defects, parents should be reassured of the relatively benign nature of the lesion, and the child should be encouraged to live a normal life. The defect may have closed spontaneously by two years of age.
- In infant with large VSD, medical management has two aims:
  1. To control congestive heart failure
  2. To prevent the development of pulmonary vascular disease
- These infants with large VSD often fail to thrive, so maintenance of normal growth is impaired.
- Congestive heart failure is treated with digoxin, diuretics, and afterload reduction medications.
- If the patient does not respond to vigorous anti-congestive measures or shows signs of progressive pulmonary hypertension, surgery is indicated without delay.

Surgical management

- Most cases of irreversible pulmonary hypertension can be prevented by surgical repair of a large defect before 2 years of age.
- Indications of surgical intervention are:
  1. **Intractable heart failure.** It needs pulmonary artery banding or surgical repair if possible during 1st year of life.
  2. **Pulmonary hypertension:** If pulmonary hypertension develops, surgical repair is necessary to prevent permanent vascular changes before 2 years of age.
  3. **Chronic volume overload** needs surgical repair between 2–5 years of age.
- Primary closure of the defect with a prosthetic patch is now used for virtually all symptomatic singular defects.

Indications of Surgery

- Failure to control CCF, despite maximum medical treatment
- Failure to thrive
- Child between 6–12 months of age with rising pulmonary hypertension
- Child with age >2 year, and pulmonary blood flow more than twice of systemic blood flow
- Supracristal VSD
- Associated pulmonary stenosis
- Development of aortic regurgitation

Prognosis

- The natural course of a VSD depends to a large degree on the size of the defect.
- 30–50% of small defects will close spontaneously, most frequently during the 1st year of life.
- The vast majority of defects that close will do so before the age of 4 years.

Complications

- Congestive heart failure
- Repeated episodes of respiratory infection
- Growth failure
- Infective endocarditis
- Pulmonary hypertension
- Eisenmenger syndrome (reversal of shunt with cyanosis)

PATENT DUCTUS ARTERIOSUS (PDA)

> CASE
>
> A 6-month-old presents for evaluation. He does well until day 6 of life, when he developed an increased respiratory rate, subcostal retractions, and a ***widened pulse pressure*** (bounding peripheral pulses). There is no cyanosis or increased oxygen requirement. A ***continuous murmur*** is heard along the left sternal border. Chest radiography shows pulmonary vascular congestion (increased pulmonary vascular markings).

- The ductusarteriosus connects the pulmonary artery and the descending aorta in the fetus, and normally closes shortly after birth.
- Patent ductusarteriosus constitutes about 10% of congenital heart defects. Patency is especially common in very low birth weight babies with pulmonary disease, and in babies with congenital rubella.
- Female to male ratio is 2:1.
- PDA persisting beyond the first few weeks of life in a term infant will rarely close spontaneously, whereas in the premature infant, if early pharmacologic or surgical intervention was not required, spontaneous closure would occur in most cases.
- An obligatory PDA is seen in 10% of patients with other congenital heart lesions.

Pathophysiology

- If ductusarteriosus remains patent after birth, blood flows from aorta to pulmonary artery (low pressure side) during systole as well as diastole, and blood returns to left side of heart.
- One half to 2/3rd of left ventricular output is shunted through the pulmonary circulation.

- Workload of left atrium and left ventricle is increased and later pulmonary hypertension may occur.
- The extent of the shunt depends on the size of the ductus and on the ratio of pulmonary to systemic vascular resistance.

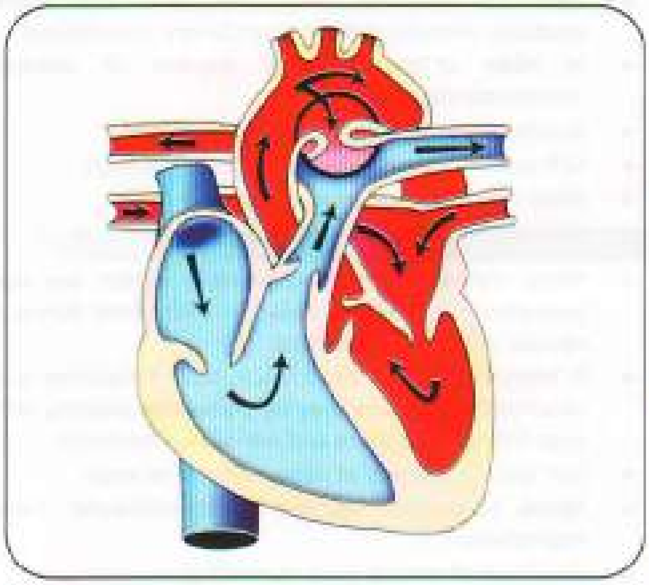


Figure 13.14: Patent ductusarteriosus

Clinical findings

- Symptoms are related to the size of the defect and the direction of flow.
- A small PDA causes no symptoms.
- A large PDA with a large left-to-right shunt may result in:
    - Congestive heart failure
    - Breathlessness while feeding
    - Slowed growth
    - Repeated lower respiratory tract infections
- Even small left-to-right shunts may cause severe compromise in low-birth-weight infants with pulmonary disease.
- If the flow is small, pulses are normal. In a large shunt, bounding pulses (with a wide pulse pressure) are palpable.
- The heart is normal in size when the ductus is small but moderately or grossly enlarged in cases with a large communication.
- The apical impulse is prominent and, with cardiac enlargement, is heaving.
- A systolic/diastolic thrill is present in the second left interspace.
- The P_2 is loud. There is systolic/diastolic (machinery) murmur around pulmonary area (second left interspace).
- If pulmonary hypertension develops then diastolic component disappears.

Diagnosis

X-ray chest

- Heart size, pulmonary vascularity, and left atrial and left ventricular size are all directly related to the magnitude of the left-to-right shunt.
- In a small PDA, the X-ray may be normal. If the PDA is large, cardiomegaly and left heart enlargement are pronounced. There are increased intrapulmonary vascular markings. Left atrial enlargement is seen as double contour of right heart border.

ECG

- ECG is normal if the PDA is small.
- Left ventricular or biventricular hypertrophy is seen if the left-to-right shunt is large.
- Right ventricular hypertrophy predominates in the presence of increased pulmonary vascular resistance.

Echocardiogram

- Echocardiogram is normal if the ductus is small.
- With large shunts, there is left atrial and ventricular enlargement and ductus can be visualized through the suprasternal notch.

Management

Medical management

- Medical closure in preterm infants is tried with indomethacin or ibuprofen.
- Dose of indomethacin is 0.2 mg/kg/dose intravenous for 3 doses 8–12 hours apart. Ductus usually closes after the first dose.
- Contraindications for indomethacin use are serum creatinine>1.7 mg/dl, thrombocytopenia, frank renal or GIT bleeding, NEC, or sepsis.

Surgical management

- If the baby is not preterm, then irrespective of age, patient with PDA require surgical closure.
- In patients with a small PDA, closure is needed to prevent endocarditis or other late complications.
- In patients with a moderate to large PDA, closure is necessary to prevent congestive heart failure and pulmonary vascular disease.
- Ligation and division of the ductus is the treatment of choice and in asymptomatic patients indicated before 1 year of age.
- Pulmonary hypertension is not a contraindication to operation at any age.

Prognosis and complications

- Patients with a small PDA may live a normal life with few or no cardiac symptoms.
- Spontaneous closure of the ductus after infancy is extremely rare.
- Main complications of PDA are:
    - Congestive cardiac failure
    - Infective endocarditis
    - Pulmonary hypertension (Eisenmenger syndrome)

ATRIAL SEPTAL DEFECT (ASD)

CASE

A 7-year-old boy presents with **exercise intolerance**. There is a prominent precordium. There is a loud first heart sound with a ***fixed and widely split second heart sound*** at the upper left sternal border that did not change with respirations. Patient is otherwise active and healthy.

- ASD (persistent patency of the inter-atrial septum) can occur:
  - High in the septum (sinus venosus defect)
  - In the mid-portion (ostiumsecundum defect)
  - Low in the septum primum (ostiumprimum defect)
- In ostiumprimum ASD, the anterior leaflet of the mitral valve is often cleft and incompetent.
- Ostiumsecundum defect is the most common form of ASD and is associated with normal atrioventricular valves.

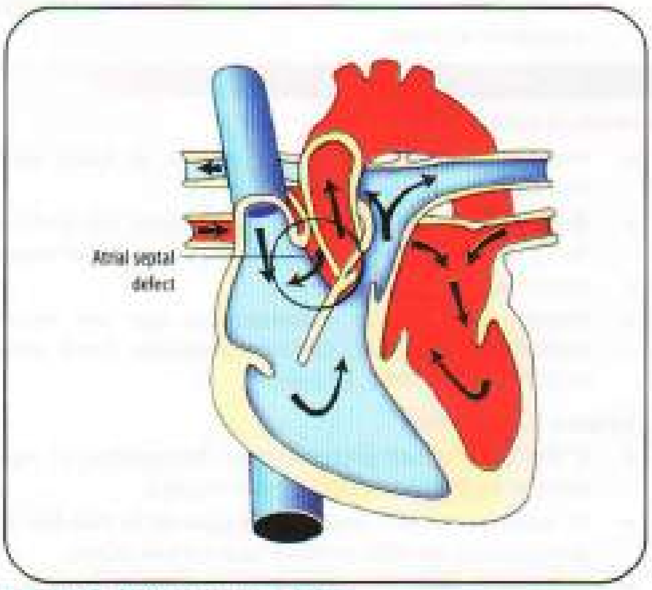


Figure 13.15: Atrial septal defect.

- An isolated patent foramen ovale is usually of no hemodynamic significance and is not considered as ASD.
- ASD represents approximately 10% of all congenital heart defects.

Pathophysiology

- Greater right than left ventricular compliance and low pulmonary vascular resistance results in a left-to-right shunt at the atrial level, thus increasing flow across the tricuspid and pulmonary valves.
- As a result, the right ventricle and the pulmonary artery are usually enlarged.
- In large defects, pulmonary blood flow is usually 2–4 times systemic blood flow.

Clinical findings

Ostiumsecundum defect

- A child with an ostiumsecundum defect is most often asymptomatic, and the lesion may be discovered on routine physical examination.
- Even an extremely large secundum ASD rarely produces clinically evident heart failure in childhood.
- In older children varying degrees of exercise intolerance may be noted.
- In ostiumsecundum defect, pulse is normal.
- Soft systolic murmur at upper left sternal edge
- Fixed split of second heart sound (S2)

Ostiumprimum defect

- Many children with ostiumprimum defect are also asymptomatic, and the defect is discovered during a routine physical examination.
- A history of effort intolerance, easy fatigability and recurrent pneumonia may be present in patients with large left-to-right shunt and mitral incompetence.
- Soft systolic murmur at upper left sternal edge
- Apical pansystolic murmur (atrioventrivcular valve regurgitation)
- Fixed split of second heart sound (S2)

Diagnosis

X-ray Chest

- Increased pulmonary vascular markings
- Cardiomegaly in large defects

ECG

- Partial right bundle branch block
- Right ventricle hypertrophy
- Superior axis in primum ASD

Echocardiogram

- The right ventricle is enlarged, and the septum often moves in a paradoxical fashion.
- The defect usually can be visualized on a two-dimensional study.

Management

Medical management

- Bacterial endocarditis prophylaxis is not necessary in secundum defects but is indicated in primum defects if mitral valve regurgitation is present.

Surgical management

- Surgery is advised for all symptomatic patients and also for asymptomatic patients with a shunt ratio of at least 2:1.
- The time for elective closure is usually at some time prior to entry into school.
- Closure is carried out at open-heart surgery.
- Mortality rate from surgery is less than 1%.

AORTIC STENOSIS

CASE

A 4-year-old girl has a murmur but is otherwise well. On examination, the pulses are normal, there is no heave, there is a systolic thrill in the suprasternal notch, and the second sound is normal with an ejection click at the mid left sternal edge and a moderately loud ***mid-systolic murmur*** at the base, maximal at the right upper sternal edge and ***radiating into the neck***.

- Valvular, subvalvular, or supravalvular aortic stenosis represents approximately 5% of all congenital heart disease.
- Lesions result from failure of development of the three leaflets or failure of resorption of tissue around the valve.

Clinical findings

- Mild to moderate obstructions cause no symptoms.
- More severe stenosis causes easy fatigability, exertional chest pain, and syncope.
- Infants with critical aortic stenosis may present with symptoms of heart failure.
- A **systolic ejection murmur**is heard at the right second intercostal space along the sternum and radiating into the neck.
- The aortic component of S2 may be decreased in intensity.

Diagnosis

Chest X-ray

- In most cases the heart is not enlarged.
- **Left ventricular hypertrophy**develops with moderate to severe stenosis
- In valvular aortic stenosis, dilation of the ascending aorta is frequently seen.

ECG (Electrocardiography)

- Patients with mild aortic stenosis have normal ECGs.
- Some patients with severe obstruction have LVH and LV strain but even in severe cases, 25% of ECGs are normal.
- Progressive LVH on serial ECGs indicates a significant obstruction.
- LV strain is an indication for surgery.

Echocardiography

- This is a reliable noninvasive technique for the evaluation of all forms of aortic stenosis.
- Doppler accurately estimates the transvalvular gradient, and the level of obstruction can be confirmed by both two-dimensional echocardiographic images and by the level of flow disturbance revealed by colordoppler.

Cardiac catheterization and angiocardi

- Left heart catheterization demonstrates the pressure difference between the LV and the aorta and the anatomic level at which the gradient exists.

Associations

- William syndrome
- Turner syndrome

Management

- Percutaneous **balloon valvuloplasty** is now standard initial treatment.
- Surgery should be considered in patients with symptoms, a high resting gradient (60–80 mmHg) despite balloon angioplasty, or coexisting aortic insufficiency.
- In many cases, the gradient cannot be significantly diminished without producing aortic insufficiency.
- Patients who develop significant aortic insufficiency require surgical intervention to repair or replace the valve.
- In the **Ross procedure**, the patient's own pulmonic valve is moved to the aortic position, and an RV-to-pulmonary artery conduit is used to replace the pulmonic valve.
- Discrete subvalvular aortic stenosis is usually surgically repaired at a lesser gradient because continued trauma to the aortic valve by the subvalvular jet may damage the valve and produce aortic insufficiency.
- Simple resection is followed by recurrence in more than 25% of patients with subvalvular aortic stenosis.

COARCTATION OF AORTA

CASE

A 16 day old infant presents with poor feeding and ***lethargy***. His birth history is normal. On examination, there is mild tachycardia, tachypnea, ***weak femoral pulses***, and a soft systolic murmur at the left sternal edge. The lungs are clear and the liver is enlarged by 3 cm.

- During development of the aortic arch, the area near the insertion of the ductusarteriosus fails to develop correctly, resulting in a narrowing of the aortic lumen.

Clinical findings

- Timing of presentation depends on the severity of obstruction and associated cardiac defects.
- Absent or diminished femoral pulses.
- Pulse lag in lower extremities.
- Upper to lower extremity systolic blood pressure gradient of >20 mmHg.Systolic blood pressure of 20 mmHg or greater in the upper than in the lower extremities.
- Blowing systolic murmur in the back or left axilla.

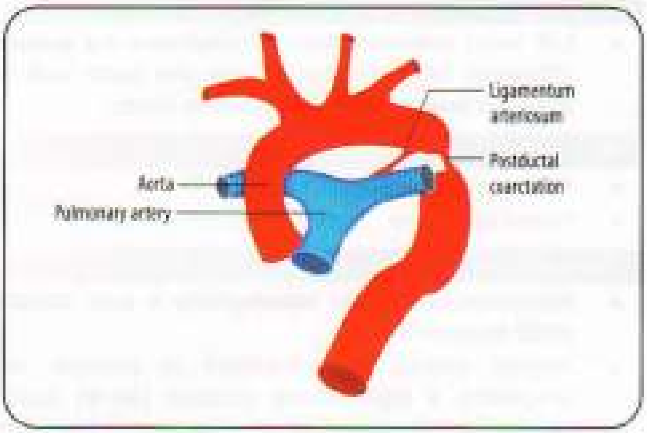


Figure 13.16: Coarctation of aorta

Diagnosis

Chest X-ray

- In the older child, radiographs may show a normal-sized heart or more often some degree of LV enlargement.
- The aorta proximal to the coarctation is prominent.
- The aortic outline may indent at the level of the coarctation.
- The poststenotic segment is often dilated.
- This combination of abnormalities results in the "figure 3" sign on chest radiograph.
- Notching of the ribs caused by marked enlargement of the intercostal collaterals can be seen.
- In patients with severe coarctation and associated heart failure, marked cardiac enlargement and pulmonary venous congestion occur.

Electrocardiography

- ECGs in older children may be normal or may show LVH.

Echocardiography

- Two-dimensional echocardiography and color-flow doppler are used to visualize the coarctation directly, and continuous-wave doppler estimates the degree of obstruction.

Cardiac catheterization and angiocardiography

- Cardiac catheterization and angiocardiography are rarely performed for diagnosis in infants or children with coarctation, but are used if transcatheter intervention is needed.
- If completed, these studies demonstrate the anatomy and severity of the coarctation and assess the adequacy of collateral circulation.

Management

- Management of an infant presenting with cardiac decompensation includes
- Intravenous infusion of **prostaglandin E1** (chemically opens the ductusarteriosus)
- Inotropic agents
- Diuretics
- Other supportive care
- **Balloon angioplasty** has been done, especially in critically ill infants, but **surgical repair** of the coarctation is most commonly performed.
- Ballooning and stenting of older patients with coarctation has become more accepted as primary therapy, but surgical repair remains a common form of management.

SUPRAVENTRICULAR TACHYCARDIA

CASE

A 7-month-old baby presents with one day history of ***pallor***, ***restlessness*** and ***breathlessness***. He has poor feeding and decreased activity. His ***heart rate*** is ***280 beats/minute***. Heart sounds are normal. Capillary refill time is 4 seconds Femoral pulses are palpable. Chest is clear. Liver is 4 cm below costal margin. ECG shows a ***narrow QRS complex***, ***no visible P waves*** and tachycardia.

- Supraventricular Tachycardia (SVT) (originating above the ventricles) is a cardiac arrhythmia arising from improper electrical activity of the heart.
- It is a type of tachycardia originating at or above the Atrioventricular (AV) node.
- It should be differentiated from ventricular tachycardias—rapid rhythms that originate within the ventricular tissue.

Clinical findings

- Common clinical findings include palpitations, shortness of breath, chest pain, respiratory distress, dizziness, syncope, irritability, pallor, and poor feeding in infants.
- The heart rate is usually between 150 and 300 beats per minute.
- Heart failure (uncommon in patients >1 year of age) is usually associated with congenital heart disease, SVT for >24 hours, and heart rates >200 beats per minute.
- The heart rate is regular and fast with a normal (narrow) QRS complex.
- Heart rate does not vary with activity.
- P wave absent or abnormal.

Common causes of SVT

- Wolff-Parkinson-White (WPW) syndrome
- Congenital heart disease
- Sympathomimetic drugs

Diagnosis

- **ECG** is the most important tool in the diagnosis of SVT.
- The rhythm is extremely regular. There is little variation in the rate throughout the entire tracing.

- The electrocardiogram in SVT typically reveals **a narrow complex tachycardia at a rate of 150–300 beats per minute** with 1:1 AV conduction and a fixed RR interval.
- The P wave may not be seen; it may be inverted just after the QRS complex; or it may precede the QRS.
- The ventricular complexes are usually normal in contour.

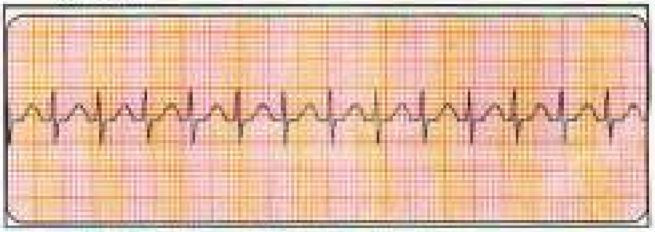


Figure 13.17: Supraventricular tachycardia.

Management

- Perform a history and physical examination.
- Carefully evaluate the patient's hemodynamic and circulatory status.
- Continuously monitor the ECG and blood pressure.
- Congestive heart failure or hemodynamic compromise is indications for rapid termination of the arrhythmia with synchronous cardioversion.
- After successful conversion to a sinus rhythm, obtain a complete ECG looking for WPW and refer the patient to a pediatric cardiologist.

For patient in shock or with hypotension

- This is a medical emergency requiring immediate Direct Current (DC) synchronized cardioversion at 0.5–2 J/kg.
- Do not wait for IV access, sedation, or intubation for the infant in shock because it will dangerously delay potentially life-saving therapy.
- When cardioverting any patient already on digoxin, consider pre-treatment with lidocain to prevent ventricular fibrillation.
- Always record the ECG during attempts at SVT termination.

For the patient with normal hemodynamics

There is a multitude of therapeutic options:

- **Vagal maneuvers:**
  - Carotid massage
  - Gag reflex
  - Valsalvamaneuvers(with the thumb in a closed mouth, have the older child blow up his or her hand)
  - The diving reflex (a bag of ice placed across the nasal bridge) works well in infants, but be cautious of hypothermia if done repeatedly.
- **Adenosine:**
  - Works extremely well to slow conduction at the AV node, breaking the re-entry cycle.
  - Although adenosine works immediately on infusion, it is very short acting (half-life of 9 seconds), which prevents its use as a preventive medication.
  - Dose is 50–250 μg/kg rapid IV bolus, followed by normal saline flush. This dose can be doubled and repeated if the first dose does not works. The maximum adult dose is 6 mg.
- Following medications slow conduction at the AV node can beused for conversion in patients who are hemodynamically stable.
- **Digoxin:**
  - Digoxin terminates SVT through its vagal effect.
  - While digoxin remains the mainstay of **treatment for chronic SVT**, it has been replaced by adenosine for acute SVT.
  - The major drawback of digoxin is the delayed onset of action; SVT may not be terminated for 6–24 hours after beginning therapy.
  - The IV Total Digitalizing Dose (TDD) is 30 μg/kg. Give one-half of the TDD initially, then one quarter of the TDD at 6–8 hours intervals.
  - Digoxin is contraindicated in patients with WPW, as it shortens the refractory period of a bypass tract in up to one-third of these patients.
- **Propranolol:**
  - Oral dosage of 1–4 mg/kg/day, with expected termination of SVT within 4–6 hours.
  - IV administration must be carefully monitored for severe hypotension and bradycardia.
  - As a negative inotrope, it should be avoided if there is any suggestion of cardiovascular compromise.
- **Verapamil:**
  - Verapamil is a calcium slow channel blocker which is extremely effective in treating SVT.
  - Oral: 2–7 mg/kg/24 hours divided q8h. Max dose: 480 mg. IV: 0.1–0.2 mg/kg q 20 minutes × 2 doses. Max dose: 5–10 mg.
  - Verapamil is contraindicated <1 year of age because of possible cardiovascular collapse.
  - Other contraindications include congestive heart failure and beta-blocker (propranolol) use.
  - Side effects may include bradycardia and hypotension.
- The need for prophylaxis against recurrence depends on many factors, including patient age, symptomatology, and patient/parental anxiety.
- Maintenance therapy is generally indicated for the first 6–12 months of life in infants with maintenance digoxin or propranolol. In older children, initiation of prophylactic medicine mainly depends on the frequency and severity of symptomatic episodes.

- If medical management fails, radio-frequency catheter ablation has been very successful at abolishing the re-entrant circuit or ectopic focus.

Prognosis

- SVT has an excellent prognosis.
- When it occurs in early infancy, 90% will respond to initial treatment.
- Approximately 30% will recur at an average age of 8 years.

CONGESTIVE CARDIAC FAILURE (CCF)

CASE

A child of 2 years of age previously diagnosed with a ***large muscular ventricular septal defect*** now presents with fatigue and poor feeding over the past month. He has not gained weight since two months. On clinical examination, he is apathetic, ***tachypneic***, and has ***wheezes and crackles on lung auscultation***. There is also ***hepatomegaly***.

Definition

- Heart failure is defined as a state in which the heart cannot deliver an adequate cardiac output to meet the metabolic needs of the body.

Pathophysiology

- Cardiac output is measured by the product of Stroke Volume (SV) and Heart Rate (HR), and increasing either of these variables may increase cardiac output.
- Cardiac output = SV x HR
- The body typically regulates its own heart rate, with tachycardia after being the first symptom of congestive heart failure.
- As the heart begins to fail, a number of local compensatory mechanisms are triggered in an attempt to maintain normal cardiac output.
- Initially, there is an increase in the activity of the sympathetic nervous system. Catecholamines cause both a more forceful contraction of the heart muscle (a positive inotropic effect) and an increase in heart rate.
- Over time, the overburdened heart may respond to increased demands by undergoing hypertrophy.
- If the combination of sympathetic activity and hypertrophy proves insufficient to expel all the venous blood that drains into the heart, end-diastolic pressure and volume increase, causing the heart to dilate.
- If the dilated ventricle is able to maintain cardiac output at a level that meets the needs of the body, the patient is said to be in *compensated heart failure*.

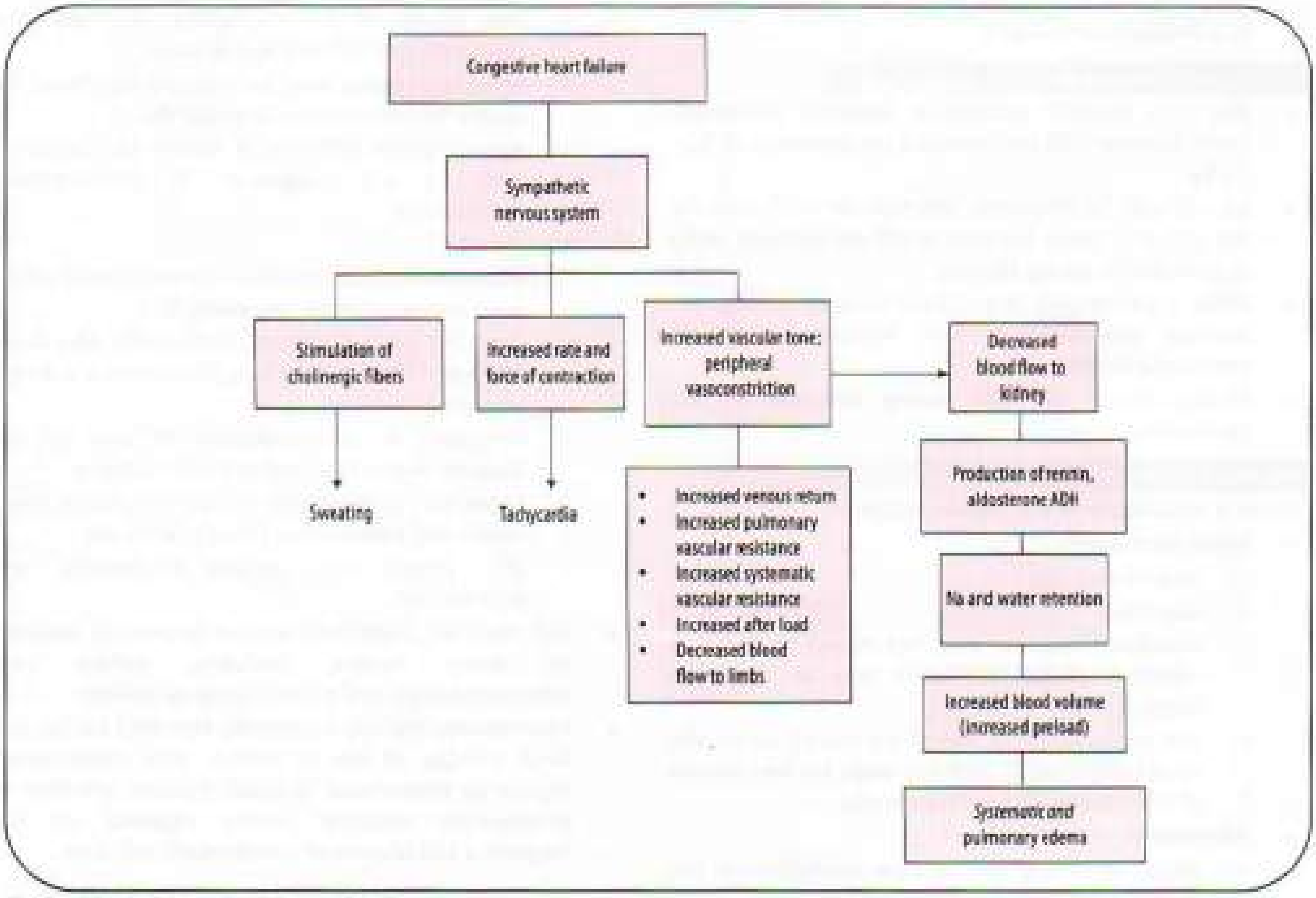

Congestive heart failure
Sympathetic nervous system
Stimulation of cholinergic fibers
Increased rate and force of contraction
Increased vascular tone: peripheral vasoconstriction
Decreased blood flow to kidney
Sweating
Tachycardia
Increased venous return
Increased pulmonary vascular resistance
Increased systematic vascular resistance
Increased after load
Decreased blood flow to limbs
Production of rennin, aldosterone ADH
Na and water retention
Increased blood volume (increased preload)
Systematic and pulmonary edema

Figure 13.18: Pathophysiology of CCF.

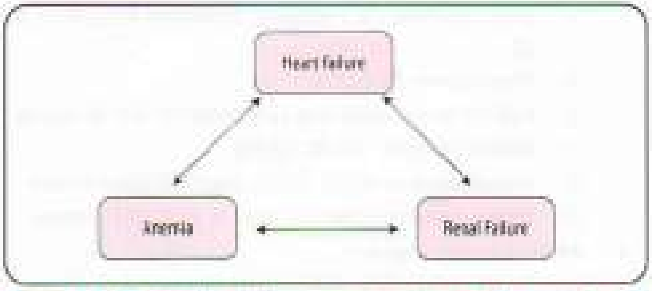


Figure 13.19: Cardiac failure in connection with anemia and renal failure.

- Beyond a certain point, however, further dilation no longer results in increased contractility, but instead leads to a progressive decrease in myocardial contractility and a decline in cardiac output. When this point is passed, patient enters a phase termed ***decompensated heart failure***.
- Cardiac failure inevitably includes an element of backward failure, the result of which is congestion of the venous circulation. In a patient with left-sided failure, this results in passive congestion of the pulmonary circulation (pulmonary edema). Congestion of the pulmonary circulation also causes an increase in pulmonary vascular resistance and, with it, an increased workload on the right side of heart, ultimately causing right heart failure. Failure of the right heart in turn contributes to the development of systemic venous congestion and soft tissue edema.

Etiology

In fetus

- Severe anemia (hemolysis, fetal-maternal transfusion)
- Supraventricular tachycardia
- Complete heart block

In neonates/infants

- Fluid overload
- Patent ductusarteriosus
- Ventricular septal defects
- Supraventricular tachycardia
- Metabolic causes–hypoxia, hypoglycemia, acidosis, anemia, and sepsis
- Asphyxiated cardiomyopathy
- Viral myocarditis
- Left-sided obstructive lesions (coarctation of aorta, hypoplastic left heart). Large mixing cardiac defects (single ventricle, truncusarteriosus)

In children

- *Rheumatic fever*
- Acute hypertension (glomerulonephritis)
- Viral myocarditis
- Cardiomyopathy
- Corpulmonale
- Severe anemia

Clinical findings

The three cardinal signs of congestive heart failure are:

1. Cardiomegaly
2. Tachypnea (left side)
3. Hepatomegaly (right side)
   - Additional signs and symptoms of congestive heart failure are:
     - Feeding difficulties
     - Dyspnea
     - Restlessness
     - Easy fatigability
     - Weak pulses
     - Pallor
     - Crepitations
     - Peripheral edema
     - Weight gain from fluid accumulation
     - Tachycardia
     - Sweating
     - Pneumonia
     - Orthopnea
     - Growth failure

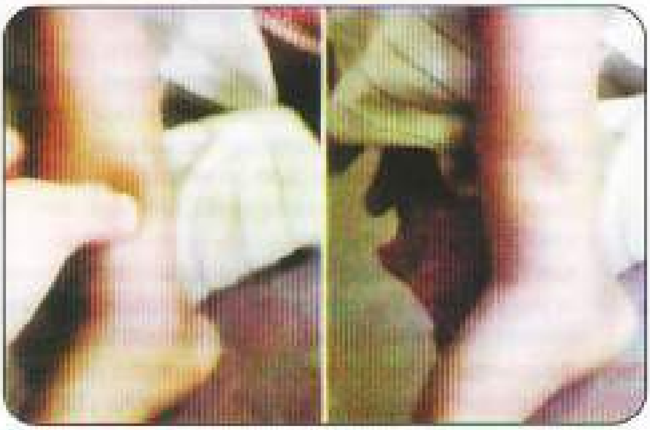


Figure 13.20: Pitting edema in CCF.

Diagnosis

X-ray chest

- X-ray chest shows cardiac enlargement.
- The pulmonary vascularity is variable depending on the etiology of the heart failure. Fluffy perihilar pulmonary markings suggestive of venous congestion and acute pulmonary edema are usually seen only with more severe degree of heart failure.

ECG

- ECG shows ventricular hypertrophy.
- *Left or right ventricular ischemic changes in* cardiomyopathies.
- Low-voltage QRS morphology with ST-T wave abnormalities suggest myocardial inflammatory disease or pericarditis.
- ECG is the best method to evaluate rhythm disorders as a cause of heart failure.

Arterial blood gases

- Arterial oxygen levels may be decreased when ventilation/perfusion inequalities occur secondary to pulmonary edema.
- When heart failure is severe, respiratory and/or metabolic acidosis may be present.

Echocardiography

- It is very useful in assessing ventricular function. Doppler studies can be used to calculate cardiac output.

Management

- The underlying cause of cardiac failure must be removed or alleviated if possible.

General measures

- **Bed rest:** Strict bed rest is rarely necessary except in extreme cases, but it is important that the child rests often and sleeps adequately.
- **Position:** Older children feel better sleeping in a semi-upright position at an angle of 20–30 degree in bed to reduce venous return.
- **Feeding:** Infants having congestive heart failure may fail to thrive because of both increased metabolic requirements and decreased caloric intake. Increasing daily calories is an important aspect of their management. Severely ill infants may lack sufficient strength for effective sucking because of extreme fatigue, rapid respiration, and generalized weakness. In these circumstances, nasogastric feedings may be helpful.
- **Salt restriction:** There is no place for salt free formulas in the treatment of congestive heart failure in infants. In older children it should be reduced to 0.5 g daily.
- If patient is admitted, then:
  - Record vital signs one hourly for the first 24 hours.
  - Maintain intake, output record.
  - Oxygen therapy given 4–6 L/minute.
  - Fluid restrictions (75 ml/kg/day or $2/3^{rd}$ of daily requirement).
  - Treat infections with antibiotics.
  - Monitor and maintain normal values of hemoglobin, calcium, potassium and pH.

Specific measures

- **Blood transfusion**: For anemia give slow packed cell transfusion 10 ml/kg.
- **Diuretics**: These relieve the edema and pulmonary congestion of heart failure.
  - Frusemide: 1–2 mg/kg/dose intravenous bolus, then 2 mg/kg/day in two divided doses.
  - Spironolactone: 1–3 mg/kg/day in two divided doses.
- **Digoxin:**
  - Digoxin is the drug of choice in congestive heart failure.
  - Digitalization (1/2 initially, followed by 1/4 q12h × 2)
  - Premature: 20 μg/kg
  - Full-term neonate (up to 1 month): 20–30 μg/kg
  - Infant or child: 25–40 μg/kg
  - Adolescent or adult: 0.5–1 mg in divided doses
  - These doses are PO; IV dose is 75% of PO dose.
- **Maintenance digoxin:**
  - 5–10 μg/kg/day, divided q12 hours
  - These doses are PO; IV dose is 75% of PO dose.
- **Features of digoxin toxicity are**: Anorexia, nausea, vomiting, and changes in the color vision. Slowing of heart rate, below 100/minute in infants, below 80/minute in young children and below 60/min in older children, indicates toxicity. Arrhythmias from ventricular extra-systoles to heart block can occur. ECG may reveal prolongation of PR interval and changes in the ST segment.
- **Treatment of digoxin toxicity**
  - Stop digoxin.
  - Ensure continuous cardiac monitoring.
  - Give KCl infusion in 5% dextrose, 0.5 ml/kg/hours (avoid in heart block).
  - Treat sinus bradycardia with atropine.
  - Phenytoin 10–15 mg loading dose is given as IV push for arrhythmia and repeat over 5–10 minutes with doubling the dose in max combined dose of 5 mg/kg.
  - For ventricular ectopics give lignocaine infusion 1 mg/kg/hour.
  - Treatment of choice is digoxin specific Fab fragment.
- Digoxin is contraindicated in renal failure.
- **Inotropic drugs:**
  Dopamine and dobutamine are used when:
  - BP is low
  - Urine output remains low
  - Response to above measures is not adequate

Dose of dopamine [illegible]

Preparation of dopamine infusion

1 ml of dopamine injection = 40 mg dopamine.

6 x body weight (kg)=amount of dopamine in mg.

Put this much amount of dopamine in 100 ml $1/5^{th}$ normal saline in a micro-burette and adjust the micro-drops according to the requirement, e.g. if 10 mg/kg/minute is to be infused then adjust the burette to 10 drops/minute. It is started in low dose and gradually increased till the good response is achieved as judged by heart rate, blood pressure and urinary flow. Initially give dopamine but if patient is not responding to 10 mg/kg/minute then change to dobutamine. Dose is same for both.

- **Vasodilators:** These reduce the after-load on the ventricles by peripheral systemic vasodilatation. These are helpful in severe terminal CCF due to left ventricular disease.

Dose

- Captopril 1.5–6 mg/kg/day in 4 divided doses
- Nitroprusside IV: 0.5–8 µg/kg/minute

INFECTIVE ENDOCARDITIS

CASE

A previously healthy 9-year-old boy presents with a ***3-week history of low-grade fever***, night sweats, fatigue, weight loss, myalgia, and headaches. On examinations, he has a ***heart murmur***, petechiae, and mild ***splenomegaly***.

Definition

- It is an inflammatory disorder of the endocardial surface, mainly of the cardiac valves, that result from infection by any of several types of microorganisms (including bacteria, fungi, and rickettsiae).

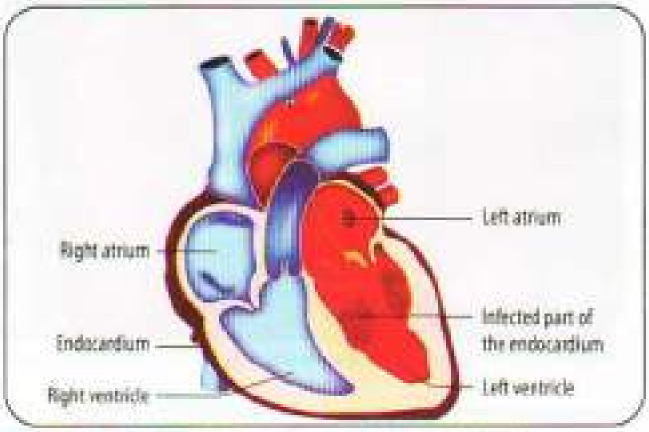


Figure 13.21: Infective endocarditis (vegetations).

Etiology

- *Streptococcus viridans* is responsible for approximately 50% of cases.
- *Staphylococcus aureus*and *Staphylococcus epidermidis* are responsible for another 30% of cases.
- Other causes are *Enterococcus*, *H. influenzae* and *Pseudomonas*.

Pathogenesis

- Although the endocardium of normal hearts may become infected, infections most commonly occur in areas of extremely turbulent flow.
- Endocarditis develops when a jet of blood, turbulence, or trauma leads to cardiac endothelial damage, which serves as a nidus for bacterial infection.
- In most cases, oral bacteria, which intermittently invade the blood stream, infect the damaged endothelium.
- Vegetations (consisting of fibrin, platelet aggregations, and bacterial masses) form on the valve leaflet. Pieces of the vegetations may break off and cause embolization (e.g. splinter hemorrhages, Roth spots).
- Some lesions that commonly are complicated by infective endocarditis include VSD, aortic stenosis, PDA, TGA, and TOF.

Clinical findings

- There may be fatigue, fever, chills, night sweats, arthralgia, malaise, chest pain, dyspnea, and myalgias.
- Signs of infective endocarditis are splinter nail bed hemorrhages, changing heart murmurs, tachycardia, arrhythmias, cardiomegaly, heart failure, splenomegaly, petechiae, weight loss, and clubbing of the fingers.
- Other findings in infective endocarditis are Roth spots (retinal hemorrhages with clear centers), Janeway lesions (flat, painless hemorrhagic macules on the hands or feet), Osler nodes (pea-sized painful nodules on the fingers).
- Metastatic infection can lead to arthritis, meningitis, pericarditis, abscesses, septic pulmonary emboli and immune complex-mediated glomerulonephritis.

Table 13.1: Modified Duke Criteria:The Clinical Criteria.

Major Criteria:
• Positive bloodculture (2 or more) • Positive echocardiogram (vegetation, paravalvularabscess, or valve dehiscence after surgery) • New valvularregurgitation (by auscultation, not echocardiogram)
MinorCriteria:
• Predisposing heart condition (including priorIE) • Injection drug use • Fever (temperature ≥100.4°F [38°C]) • Major arterial emboli • Septic pulmonary infarcts • Mycotic aneurysm • Intracranial hemorrhage • Conjunctivalhemorrhage • Janeway lesions (painless hemorrhagic lesions onpalms and soles) • Glomerulonephritis • Osler nodes(painful lesions at fingertips) • Roth spots (retinal hemorrhages) • Positive rheumatoid factor • Single positive blood culture • Serologic evidence of active infection with an "organism consistentwith IE"
Definite IE:
• Pathologic evidenceof intracardiac or embolized

vegetation or intracardiac abscess.OR

- Clinical criteria: Two major, or one major and threeminor, or five minor criteria.

Diagnosis

- ESR is usually raised. Leukocyte count may be normal or raised.
- There may be microscopic hematuria.
- Blood cultures are critical for diagnosis. At least three blood cultures should be obtained within 24 hours.
- Echocardiography localizes the vegetations.

Management

- If untreated, infective endocarditis is almost always fatal.
- IV antibiotic therapy for 4–6 weeks is necessary:
  - Benzyl Penicillin *or* Ceftriaxone + Gentamicin (for streptococcus).
  - (Penicillin 200,000 U/kg per 24 hours IV in 4–6 equally divided doses; ceftriaxone 100 mg/kg per 24 hours IV, gentamicin 3 mg/kg per 24 hours IV in 1 dose or 3 equally divided doses)
  - Vancomycin 40 mg/kg per 24 hours IV in 2–3 equally divided doses. Vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone.
  - Vancomycin is also recommended for staphylococcus for 6 weeks. Other recommendations for staphylococcus are nafcillin or oxacillin or cefazolin.
- Surgical treatment may be required for removal of vegetations or valve replacement.

Prophylaxis (prevention)

- The use of antibiotics before and during any surgical procedure that can cause a transient bacteremia in susceptible children prevents infective endocarditis.
- The antibiotic regimen to prevent endocarditis during dental or respiratory procedures is oral amoxicillin and for gastrointestinal or genitourinary manipulation, oral amoxicillin or parenteral ampicillin and gentamicin. Clindamycin is indicated for most patients allergic to penicillin.

Complications

- Congestive cardiac failure due to valvular dysfunction
- Myocardial abscesses
- Pulmonary emboli
- Aneurysm formation

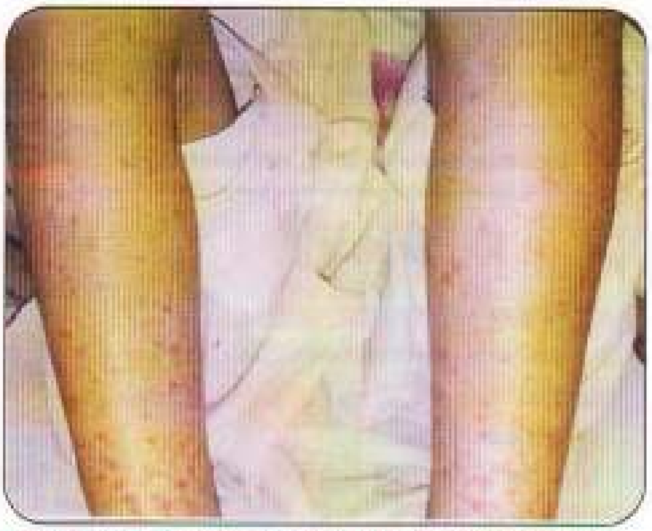


Figure 13.22: Characteristic rash in infective endocarditis.

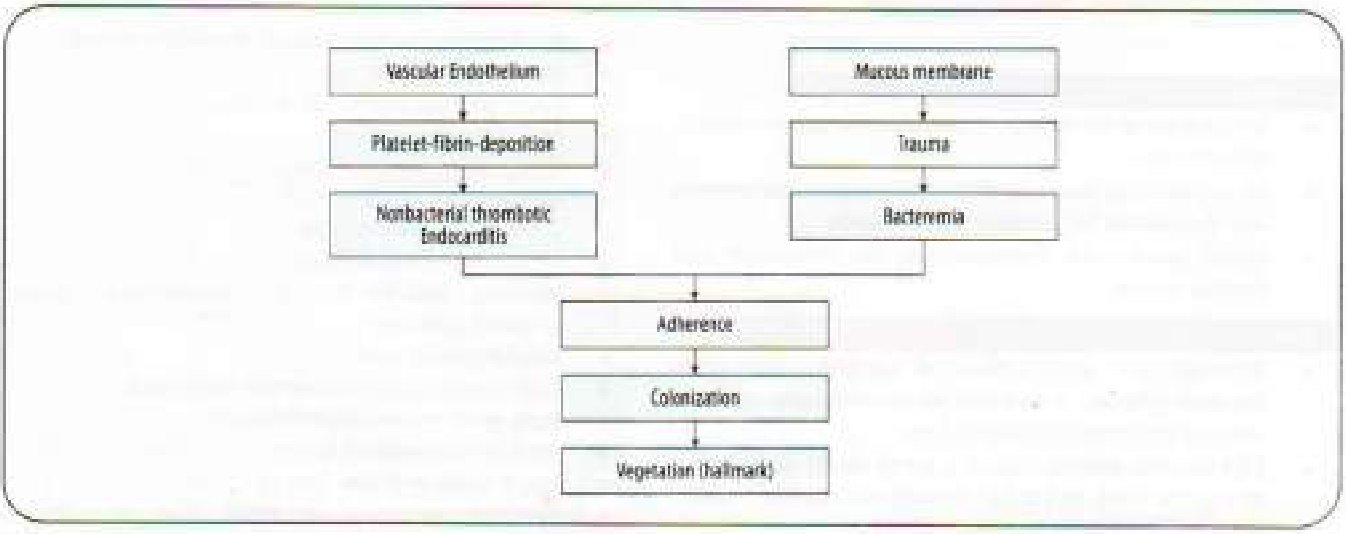


Figure 13.23: Pathophysiology of infective endocarditis.

CARDIOMYOPATHY

CASE

Hypertrophic cardiomyopathy: A 15-year-old boy presents with ***occasional shortness of breath*** and ***dizziness during exercise***, with ***occasional chest pain***. There is history of ***loss of consciousness*** once last month during playing football. His ***grandfather died suddenly*** at age 37 of unknown cause. Otherwise all family is healthy.

Definition

- Cardiomyopathy is defined as the dysfunction of myocardium (the muscle of the heart).

Types

Primary

- Dilated or congested cardiomyopathy
- Hypertrophic cardiomyopathy
- Restrictive cardiomyopathy

All three manifest clinically by heart failure, chest pain, dyspnea, arrhythmias, or sudden death.

Secondary

- Infections
- Metabolic
- Sensitivity and toxic reactions

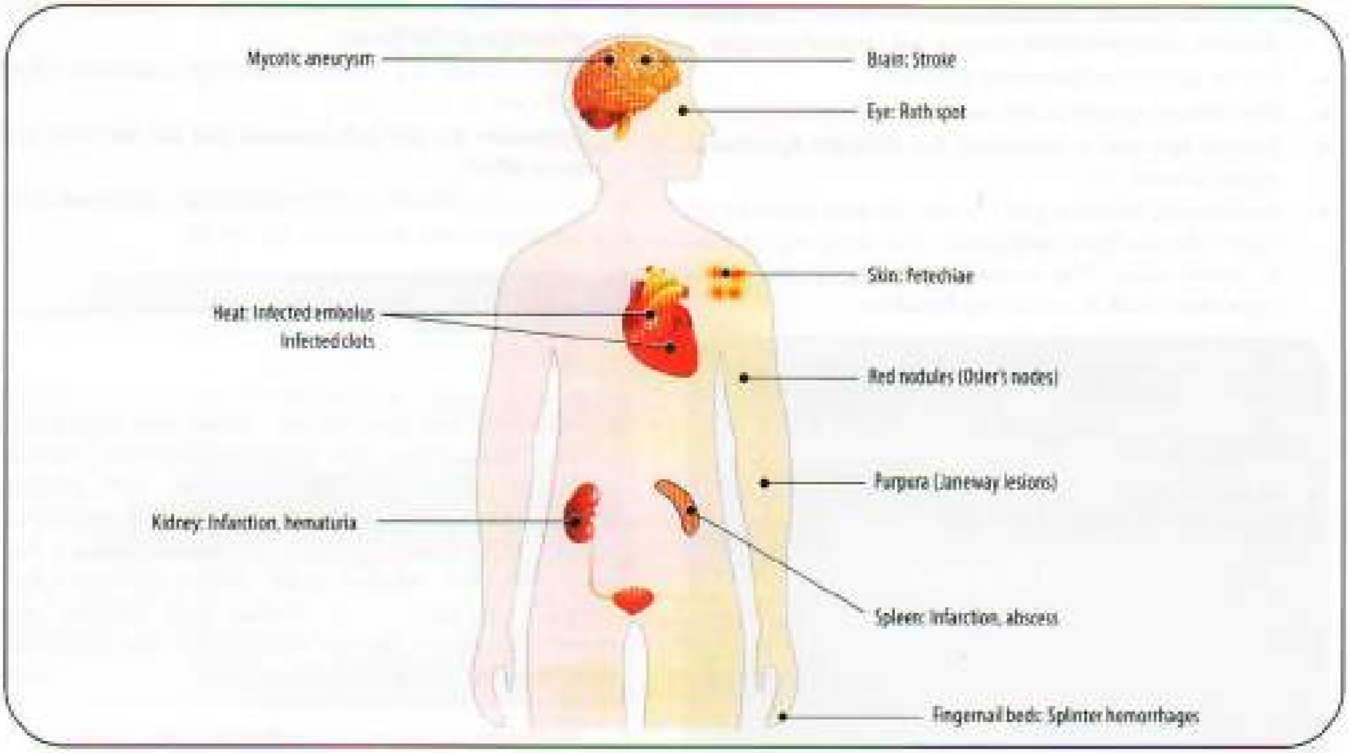

Mycotic aneurysm
Brain: Stroke
Eye: Roth spot
Skin: Petechiae
Heat: Infected embolus
Infected clots
Red nodules (Osler's nodes)
Purpura (Janeway lesions)
Kidney: Infarction, hematuria
Spleen: Infarction, abscess
Fingernail beds: Splinter hemorrhages

Figure 13.24: Characteristic findings in infective endocarditis.

Dilated cardiomyopathy

- Congestive or dilated cardiomyopathy is characterized by myocardial dysfunction and ventricular dilatation.
- Failure of the left ventricle function results in an increase in end-diastolic volume. It leads to increased left atrial, pulmonary venous and pulmonary capillary pressures.
- Mitral valve regurgitation may result from papillary muscle dysfunction or from severe dilatation of the valve annulus.
- Although dilated cardiomyopathy usually is a primary disorder, it may be associated with neuromuscular disease (e.g. Duchenne muscular dystrophy) or result from drug toxicity (e.g. doxorubicin).

Clinical findings

- There may be dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, and bronchospasm (due to left heart failure).
- Dependent edema may be present (due to right heart failure).
- There may be tachypnea, tachycardia, a right ventricular heave, prominent P_2, gallop rhythm, and murmurs of mitral or tricuspid valve regurgitation.
- There may be low blood pressure, narrow pulse pressure, and pulsusalternans.

Investigations

- Chest X-ray shows cardiomegaly and pulmonary venous congestion.

- ECG shows left ventricular hypertrophy and rhythm disturbances.
- Echocardiography is diagnostic defining the left ventricular function.

Management

- Inotropic agents are used to improve left ventricular function.
- Vasodilators are used to unload the left ventricle.
- Diuretics are used to decrease preload.
- Anti-arrhythmic medications are used for rhythm disturbances.
- In refractory cases, cardiac transplantation may be needed.

Hypertrophic cardiomyopathy

- It is also called idiopathic hypertrophic sub-aortic stenosis or hypertrophic obstructive cardiomyopathy.
- It is an autosomal dominant disorder.
- The septum as well as left ventricle wall is thickened.
- Systolic function is preserved but diastolic function is compromised.
- Asymmetric thickening of the septum may result in left ventricular outflow obstruction and abnormal motion of mitral valve. This abnormal motion of the mitral valve may result in mitral regurgitation.

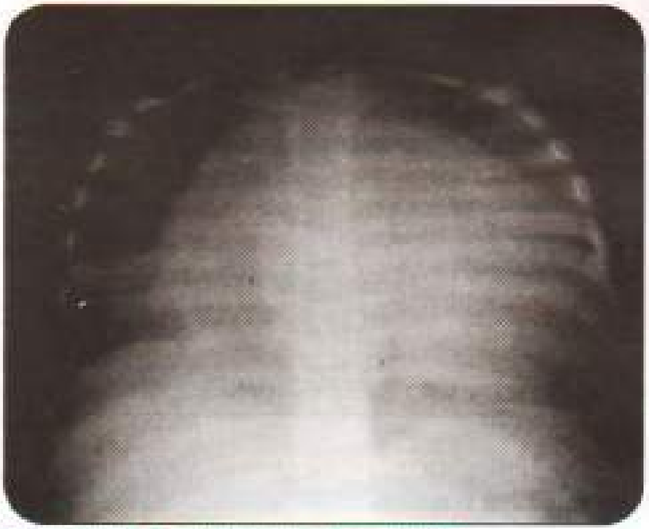


Figure 13.25: X-ray Dilated cardiomyopathy

Clinical findings

- There may be dyspnea on exertion (due to decreased cardiac output), chest pain (due to myocardial ischemia), syncope and death (due to rhythm disturbances).
- On physical examination, pulse often is biferious (double peaked), and there is a murmur of mitral regurgitation.

Investigations

- ECG shows left axis deviation, left ventricular hypertrophy, ST segment depression, and T-wave inversion.
- Echocardiography is diagnostic and demonstrates asymmetric hypertrophy of septum.

Management

- Negative inotropic medications (calcium channel blockers, beta blockers) are used to decrease left ventricular stiffness.
- Fatal arrhythmia should be prevented, and competitive exercises should be avoided.

Restrictive cardiomyopathy

- It is a disorder characterized by a primary decrease in ventricular compliance, resulting in impaired ventricular filling during diastole.
- It is a less common disorder than other types of cardiomyopathies.
- The most common cause is a disease called endomyocardial fibrosis.
- Other causes are hemochromatosis, radiation injury, and cardiac amyloidosis.
- Ventricles are stiff and inelastic that can be filled with great effort.
- Patient has fatigue, exertionaldyspnea, and chest pain.
- Treatment with diuretics is beneficial.

MYOCARDITIS

CASE

A 2-week-old boy presents with ***pallor*** and respiratory distress. Respiratory rate is 80 breaths per minute (***dyspnea***). Heart rate is 195 beats per minute (***tachycardia***). Heart sounds are ***distant***, and a gallop is heard. On X-ray, there is cardiomegaly. An echocardiogram shows poor ventricular function, dilated ventricles, and dilated left atrium. An electrocardiogram shows ventricular depolarization complexes that have ***low voltage***.

- Myocarditis refers to inflammation, necrosis, or myocytolysis.
- It may be caused by many infectious, connective tissue, granulomatous, toxic, or idiopathic processes affecting the myocardium.
- There is no involvement of the endocardium or pericardium.
- The most common manifestations are heart failure, arrhythmias and sudden death.
- Viral infections are the most common cause. The most common causative agents in children are adenovirus, coxsackievirus B, and other enteroviruses.

Pathophysiology

- Acute viral myocarditis may produce a fulminant inflammatory process (cellular infiltrates, cell degeneration and necrosis, and subsequent fibrosis).

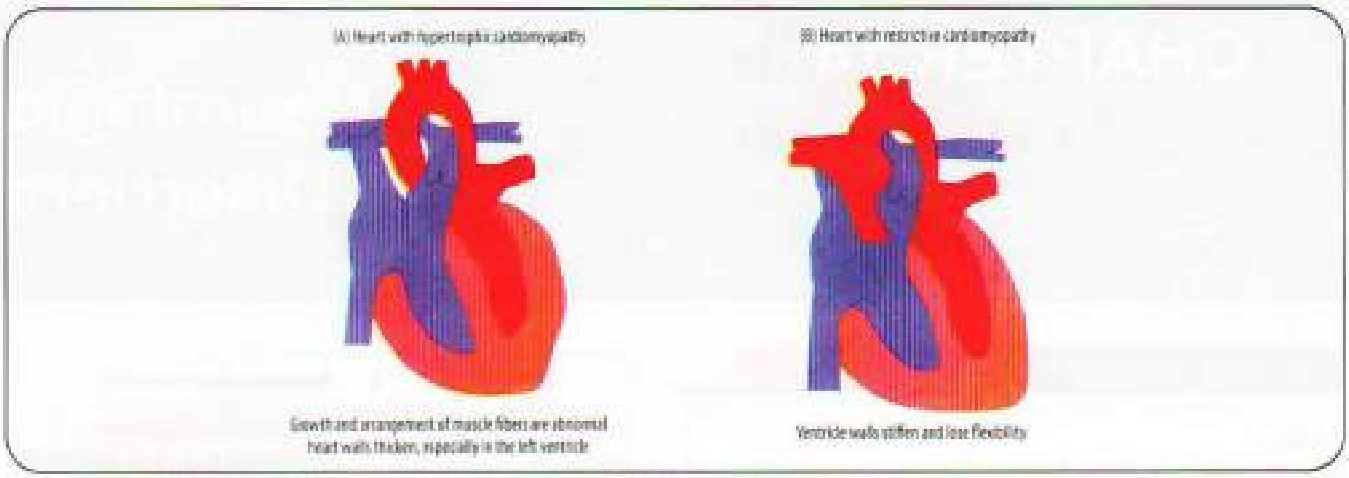

(A) Heart with hypertrophic cardiomyopathy
(B) Heart with restrictive cardiomyopathy
Growth and arrangement of muscle fibers are abnormal
heart walls thicken, especially in the left ventricle
Ventricle walls stiffen and lose flexibility

Figure 13.26: (A) Heart with hypertrophic cardiomyopathy (B) Heart with restrictive cardiomyopathy

Clinical findings

- Signs and symptoms depend on:
    - Patient's age
    - Acute or chronic nature of the infection

In neonates

- Fever, severe heart failure, respiratory distress, cyanosis, distant heart sounds, weak pulses, tachycardia out of proportion to the fever, mitral insufficiency caused by dilatation of the valve annulus, a gallop rhythm, acidosis, and shock.

In older child

- An older child may present with acute congestive heart failure or a sudden onset of ventricular arrhythmias.

Diagnosis

- ESR (erythrocyte sedimentation rate) are raised.
- Heart enzymes (creatine phosphokinase, lactate dehydrogenase) are raised.
- Brain Natriuretic Peptide (BNP) is raised.
- Serum viral titers may be positive.
- Chest X-rays in severe, symptomatic cases reveal cardiomegaly, pulmonary vascular prominence, overt pulmonary edema, or pleural effusions.
- Cardiac MRI is a standard imaging modality for the diagnosis of myocarditis.
- Echocardiography demonstrates poor ventricular function and often a pericardial effusion, mitral valve regurgitation, and the absence of coronary artery or other congenital heart lesions.
- Myocarditis can be confirmed by endomyocardial biopsy (although not without risk). Biopsy is performed during cardiac catheterization and can also be used to detect other causes of cardiomyopathy (storage disease, mitochondrial defects).
- PCR can identify specific viral RNA or DNA.

Differential diagnosis

- Carnitine deficiency
- Hereditary mitochondrial defects
- Idiopathic dilated cardiomyopathy
- Pericarditis
- Fibroelastosis of the endocardium
- Anomalous origin of the left coronary artery

Management

- Supportive measures for severe congestive heart failure or cardiogenic shock.
- Dopamine, epinephrine, and milrinone may be helpful in poor cardiac output and systemic hypoperfusion.
- All inotropic agents, including digoxin, should be used with caution in myocarditis because of the arrhythmogenic properties of these agents. When used, digoxin should be given at half the normal dosage.
- Pericardiocentesis should be performed in patients with evidence of cardiac tamponade.
- Arrhythmias should be treated aggressively with intravenous amiodarone to achieve adequate control.
- For infants and children in cardiogenic shock, Extracorporeal Membrane Oxygenation (ECMO) may be indicated.
- Heart transplantation is the treatment of choice in those with refractory heart failure.
- Intravenous Immunoglobulin (IVIG) has been used at 2 g/kg.
- Treatment with prednisone (2 mg/kg daily, tapered to 0.3 mg/kg daily over a period of 3 months) is effective in reducing myocardial inflammation and improving cardiac function.

Prognosis

- *The outcome of symptomatic neonates with acute viral myocarditis is poor.*
- Patients with lesser symptoms have a better prognosis, and complete resolution may occur.
- The outcome of older patients who have progressed to chronic dilated cardiomyopathy is also poor without therapy.

CHAPTER 14

Neurologic Disorders

PYOGENIC MENINGITIS

CASE

A previously well 4-year-old child presents with a ***high-grade fever*** 104°F (40°C), ***headache***, and ***stiff neck***. There is a 3-day history of upper respiratory tract symptoms and vomiting. Kernig and Brudzincki signs are positive.

- Bacterial meningitis is an important and serious infection in childhood.

Definition

- **Meningitis** is defined as inflammation of the membranes surrounding the brain and spinal cord, including the dura, arachnoid, and pia mater.
- **Meningoencephalitis** represents inflammation of both the meninges and the cortex of the brain.

Incidence

- Bacterial meningitis occurs at all ages but is commonest in infancy.
- Meningitis may result in death of the child within hours of the onset of the disease if untreated.
- It is responsible for about 3% of hospital admissions in children.
- It occurs more frequently in males than females during infancy.

Etiology

- This depends upon the age of the patient and host resistance.
- It should be known that any organism could cause meningitis.
- Greatest risk for meningitis is between 6 to 12 months of age and 95% of cases occur between 1 month and 5 years of age.
- Causative agents responsible at various ages are given in table below:

Table 14.1: Causative agents responsible at different ages.

Age	Causative agents
0–2 months	• **Escherichia coli** • Group B streptococci • Staphylococcus aureus. • Listeria monocytogenes
2 months–2 years	• **Hemophilus influenza type b** • Streptococcus pneumonia • Neisseria meningitides
2 years–21 years	• **Neisseria meningitides** (serotypes A, B, C, Y, and W135) • **Streptococcus pneumonia** (serotypes 1, 3, 6, 7, 14, 17–19, 21, 23) • H. influenzae

Pathogenesis

- Inflammation of the meninges (meningitis) is initiated when cell wall and membrane products of an organism disrupt the blood-brain barrier (capillary endothelium of the CNS).
- The causative organism may enter the CNS by hematogenous spread or by direct invasion.
- Hematogenous spread to the meninges may occur with infective endocarditis, pneumonia, or thrombophlebitis. Bacterial invasion from a contiguous focus of infection (sinusitis, mastoiditis, osteomylitis of the skull) may occur. Anatomic defects secondary to trauma (e.g. fracture in cribriform plate) or congenital defects should be suspected in the recurrent meningitis.
- Bacterial invasion of the CSF is followed by an outpouring of polymorphs and fibrin. There is a cascade of events involving cytokines and chemokines released within the CNS. These inflammatory mediators are stimulated by the bacterial cell wall and membrane elements. As a result the meninges becomes inflamed, swollen and covered with exudate. This exudate is most marked in pneumococcal meningitis. In pneumococcal meningitis it is over the frontal lobes and vertex. The cerebral vessels and cranial nerves may be involved in the purulent exudate at the base of brain and can lead to permanent neurologic damage. Early in illness there is cerebral edema and ventricles are reduced in size.
- Meningeal signs are due to inflammation of the spinal nerves and roots.
- Pressure on the peripheral nerves may lead to motor or sensory deficit.
- Deafness, vestibular disturbances, and optic nerve involvement are common due to inflammation or swelling of cranial nerves.
- Communicating (non-obstructive) hydrocephalus is due to adhesive thickening of the arachnoid in the basal cisterns.

- Obstructive hydrocephalus is due to fibrosis or gliosis obstructing the aqueduct of Sylvius or the foramina of Magendie and Luschka.
- Cerebral atrophy is due to thrombosis of small cortical veins resulting in necrosis of the cerebral cortex. Total cerebrum dissolution may occur from cerebral necrosis secondary to obliteration of veins and arteries, and a combined increase in intraventricular pressure.
- Inflammation involving the veins that cross the subdural space and capillaries found in the dura lead to an increase in vascular permeability and loss of albumin-rich fluid into the subdural space (increasing protein level in CSF).
- Hypoglycorrhachia (hypoglycemia in CSF) is due to decreased transport of glucose across the inflamed choroids plexus, and increased glucose use by the host.
- Seizures are due to depolarization of neuronal membranes as a result of cellular electrolyte imbalance.
- Following antibiotic administration, rapid bacterial lysis results in release of bacterial cell wall and membrane fragments (e.g. lipopolysaccharides), causing an enhanced inflammatory response and further elevation of intracranial pressure.
- Dexamethasone administration before the first dose of antibiotics modulates the enhanced meningeal inflammatory response by inhibiting the effects of tumor lysis factor and interleukin-1.
- The most frequent sequelae associated with meningeal inflammation is sensorineural hearing loss.

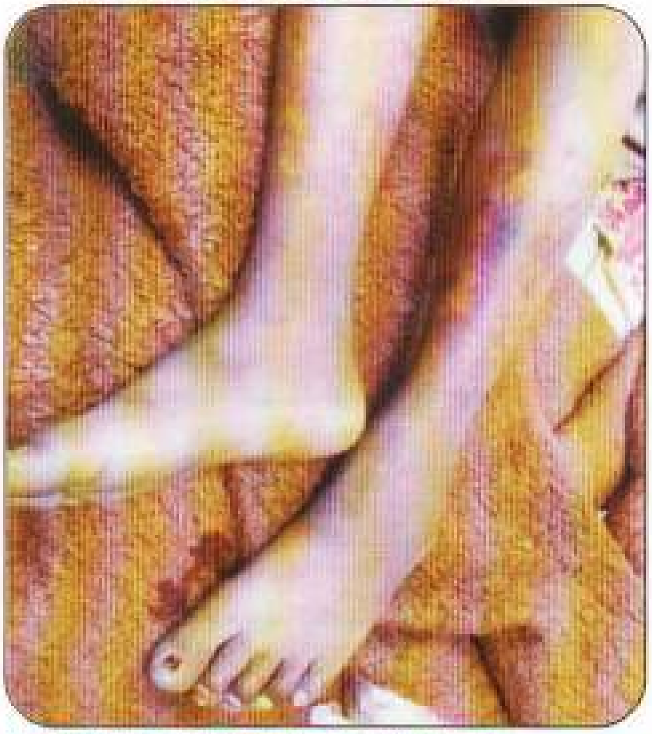


Figure 14.1: Rash in meningococcal meningitis.

Clinical findings

- Meningitis always must be considered in any young infant whose temperature is greater than 100.7°F (38.2°C) and who has no obvious site of infection.

Neonates

- Gram negative organisms are commonly responsible for meningitis.
- Infective illness in the mother, prolonged rupture of membranes or difficult delivery put the newborn at risk.
- Premature infants have low level of placentally transmitted immune antibodies.
- Common predisposing factor is spina bifida or dermal sinus.
- In neonates initial signs may be subtle and non-specific.
- Fever occurs in 50% of infected infants.
- Infant does not look well and feeds poorly. Infant may develop hypothermia, vomiting, irritability, lethargy and convulsions.
- Bulging of anterior fontanel, head retraction and a high-pitched cry are signs of established meningitis.

Older children

- Classics signs of meningitis are preceded by upper respiratory or GIT symptoms.
- Meningeal inflammation leads to high-grade fever, headache and projectile vomiting.
- Seizures are common (occur in 20–30% of patients before or during the first 3 days after diagnosis of meningitis). Seizures early in the disease course usually result from inflammation and edema and do not signify an adverse outcome. Seizures that are difficult to control or persist beyond the fourth hospital day are significant and have a bad prognosis.
- Increased CSF pressure leads to bulging of fontanel and diastasis of sutures in infants.
- There is neck stiffness, positive Kernig's (flexion of the leg 90^0 at the hip with pain on extension of the leg thereafter) and Brudzinski's signs (involuntary flexion of the legs when the neck is placed in flexion).
- Cranial nerve palsies (6^{th} commonest) and papilledema may be present.
- Hemiplegia may be present in those who report late in illness.
- Ataxia may also be a presenting sign.
- Patient may present in semi-comatose or comatose condition. This is more common in pneumococcal or meningococcal than H. influenzae meningitis.
- Meningococcal meningitis is characterized by the presence of generalized purpuric rash, purple mottling of the skin, peripheral cyanosis and child looks toxic and comatose. The heart rate is very rapid, blood pressure is unrecordable and respiration Cheyne-Stokes. Child may develop disseminated intravascular

coagulation and may die during acute stage. This is called Waterhouse Friederichsen syndrome.

- Otitis media or mastoiditis is likely to lead to streptococcal or pneumococcal meningitis.
- Staphylococcal infection is likely following surgical procedures, skull fracture or skin infection.
- If there are no specific signs between 6 months to two years of age, H. influezae is the causative organism.
- Onset of clinical signs and symptoms of meningitis is sudden (within 24 hours) in meningococcal and S. pneumonia infection. Course is subacute (2–3 days) with H. influenzae.

Diagnosis

Lumbar Puncture (LP)

- During a lumbar puncture, CSF pressure should be noted.
- When Intracranial Pressure (ICP) is elevated, the minimum amount of CSF (necessary for all important laboratory tests) should be removed.
- Color of the CSF should be noted. Xanthochromia (yellow color of CSF) is present due to jaundice, bilirubin from hemorrhage, or increased CSF protein.
- CSF is sent immediately for examination including total leukocyte count and a differential count on a wright-stained smear.

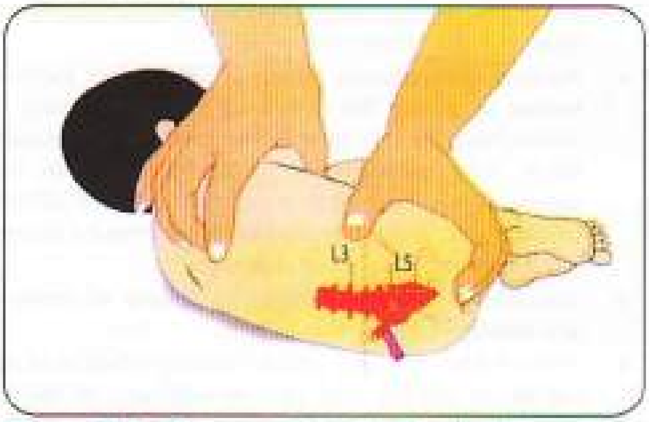


Figure 14.2: Recommended site for lumbar puncture (Between L3 and L5).

- If the lumbar puncture is traumatic, one leukocyte per 700 red blood cells in the CSF is subtracted; and one additional mg protein is added in CSF protein for 800 red blood cells.
- Glucose in the CSF should be compared to the blood glucose obtained just before the lumbar puncture. Normally, CSF glucose is greater than $2/3^{rd}$ of the blood glucose. In bacterial meningitis, CSF glucose concentration less than $2/3^{rd}$ of the blood glucose concentration is the rule.
- In CSF of neonates, normally there are up to 30 lymphocytes, and normally there is up to 150 mg/dl protein (65 mg/dl at 6 months).

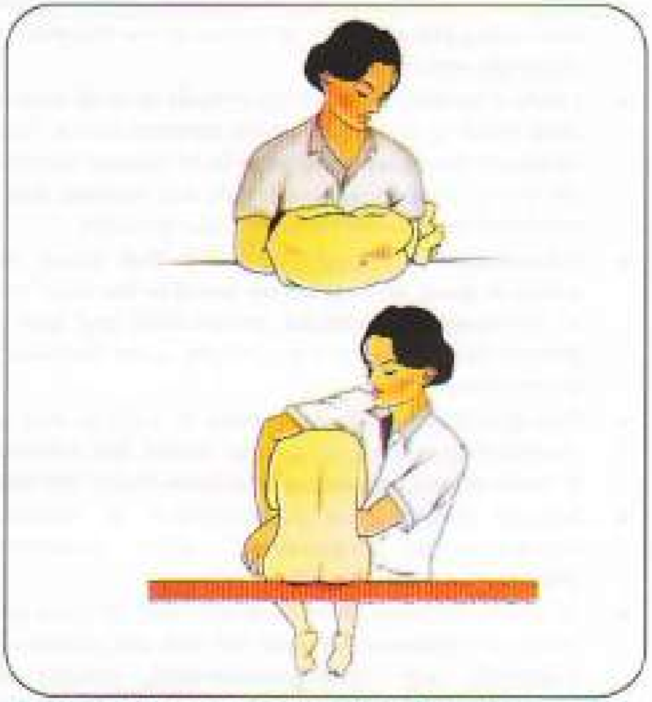


Figure 14.3: Recommended positions for lumbar puncture.

- Gram stain is also important to recognize the causative organism.
- Before lumbar puncture is performed, the fundi should always be checked for papilledema.

Table 14.2: CSF findings in various CNS disorders.

Condition	Color	Leukocytes/mm^3	Protein (mg/dl)	Glucose (mg/dl)
Normal	Clear	0–5; 60–75% lymphocytes.	20–45	>50 or 75% of blood glucose
Acute bacterial meningitis	Opalescent to purulent	100–10,000+; PMN predominate	100–500	<40; or <50% of blood glucose
Tuberculous meningitis	Opalescent	10–500; PMN early but lymphocytes predominate later	100–3000	<40; may be none
Viral encephalitis	Clear	None to a few hundred; mostly lymphocytes; PMNs predominate early	20–100	Generally normal

Table 14.3: Gram staining.

Gram staining	
Meningococci	Gram-negative intracellular diplococci
Pneumococci	Gram-positive diplococci
H. influenzae	Gram-negative coccobacilli
E. coli	Gram-negative bacilli

Table 14.4: Contraindications for an immediate LP.

Contraindications for an immediate LP

- Increased Intracranial Pressure (ICP) especially when there are focal neurologic deficits.
- Severe cardio-pulmonary compromise.
- Infection of the skin overlying the site of LP.
- Bleeding or clotting disorder.

CSF culture

- The yield of bacterial CSF cultures decreases soon after antibiotic therapy has been started. More sensitive technique, Polymerase Chain Reaction (PCR) may help to diagnose cases of bacterial meningitis in patients pre-treated with antibiotics.

Blood counts

- Total and differential leukocyte counts: Generally there is leukocytosis with predominant polymorphs.

Blood culture

- Blood culture results are positive in almost 90% of the patients with *H. influenzae* meningitis and 80% of the patients with *S. pneumonia* meningitis. 90% of patients with meningococcal meningitis also have positive blood culture results.

X-ray chest

- To rule out pneumonia, tuberculosis

CT Scan

Table 14.5: Indications for CT Scan in a patient with meningitis.

- Newborn (except for disease caused by Listeria)
- Prolonged comatose condition
- Seizures 72 hours after start of treatment
- Continued excessive irritability
- Focal neurologic findings
- Persistently abnormal CSF findings
- Relapse or recurrence

Rapid diagnostic tests

- Countercurrent Immuno-Electro-Phoresis (CIE)
- Latex Particle Agglutination (LPA) tests
- Enzyme-Linked Immuno-Sorbent Assay (ELISA) is used to detect bacterial antigen in CSF
- CSF lactate (LDH) level is also increased in bacterial meningitis (>24 units/l)
- Enzyme radioisotope assay to detect activity of β-lactamase in CSF

Gram staining

- Gram staining of smears of petechial or purpuric lesions (if present) on the skin. These smears may reveal the causative organism especially meningococci.

Different diagnosis

- Tuberculous meningitis
- Aseptic meningitis
- Brain abscess
- Brain tumor
- Cerebral malaria

Management

Supportive measures

- The first 3 to 4 days of treatment of bacterial meningitis are the most critical and so need intensive supportive measures.
- Vital signs should be recorded every 15–30 minutes until the patient is stable. Then, they should be recorded after every hour for 2–3 days.
- Frequent neurologic assessment is indicated including pupillary reflexes, level of consciousness, cranial nerve signs, and evaluation for seizures.
- Measure head circumference daily in children less than 18 months of age.
- Strict intake output record is needed.
- Patient's body weight and serum electrolytes are monitored initially 12 hourly then daily.
- Control temperature with water sponging and antipyretics.
- Feeding should be continued and give tube feeding if necessary. Initially, the patient should receive nothing by mouth. NG feeding is started when patient is stable.
- Fluids–Restricted to 60–75% (800–1000 ml/m^2/day) for fear of inappropriate ADH secretion. Fluid restriction is not indicated in the presence of hypotension because this may cause decreased cerebral perfusion pressure causing CNS ischemia.
- Care of comatose patient, e.g. bowel, bladder, skin, posture, mouth, and airway care.
- Seizures are common in a patient with meningitis. For seizures IV diazepam 0.1–0.2 mg/kg/dose is given. After immediate management of seizures, phenobarbitone or phenytoin is given regularly to prevent recurrence of seizures. Loading dose of phenobarbitone is 10 mg/kg; maintenance dose is 5 mg/kg/day in 2 divided doses.

Specific measures

Antibiotics

- When bacterial meningitis is suspected and after all cultures are obtained, appropriate antibiotics on the basis of age and epidemiologic factors must be initiated.

- Term infants in the first month of life are treated with a combination of ampicillin with either gentamicin or cefotaxime.
- For low birth weight preterm infants in the nursery who present with late-onset meningitis, an anti-staphylococcal agent such as vancomycin and an aminoglycoside are used until culture results are available.
- For infants 1 to 2 months of age, ampicillin and cefotaxime or ampicillin and ceftriaxone provide coverage against enterococci and *Listeria* as well as the normal pathogens beyond the newborn period.
- Resistant strains of *S. pneumonia* are a worldwide problem among infants and children 2 to 3 months of age. The routine dose of cefotaxime or ceftriaxone used alone for meningitis is not sufficient to clear these organisms from CSF. So, initial meningitis therapy must include vancomycin in dose of 60 mg/kg/day in four divided doses in addition to either cefotaxime or ceftriaxone.
- Alternative drug is meropenem 120 mg/kg/day IV divided in three doses.
- The duration of antibiotic therapy for meningitis depends on the causative agent and clinical response to therapy. Minimum duration of therapy for *H. influenzaetype b* and *S. pneumonia* meningitis is 10 days. Minimum duration of therapy for meningitis due to N. meningitides is 7 days. Prolonged therapy is required in case of some complications such as subdural empyema, delayed sterilization of CSF, prolonged fever, persistent signs of meningeal irritation, or development of nosocomial infections.

Steroids

- Dexamethasone in a dose of 0.6 mg/kg/day in 2–4 divided doses for 2–4 days is recommended. It decreases meningeal inflammation and sensorineural hearing loss. The first dose of steroid preferably is given before or concurrent with the first dose of antibiotic. Administration of dexamethasone 15–30 minutes after the first antibiotic dose is likely not to be beneficial because once the cytokine cascade has been initiated by the lytic effect of antibiotics on the organism; steroids cannot modulate the meningeal inflammatory cascade.

Table 14.6:Dose of antibiotics recommended in meningitis.

Antibiotic	**Dose**
Ampicillin	In neonate: 100–200 mg/kg/day divided every 6–12 hours. In children: 200-400 mg/kg/day divided every 6 hours.
Cefotaxime	In neonates: 100–150 mg/kg/day divided every 6–8 hours. In children: 200 mg/kg/day In divided doses after every 6–8 hours.
Ceftriaxone	100 mg/kg at diagnosis, then after 12 hour. Then 100 mg/kg/day in divided doses after every 12 hours or as a single dose every 24 hours.
Gentamicin	In neonate: 5 mg/kg/day in divided doses after every 12 hours. In children: 7.5 mg/kg/day in divided doses after every 8 hours.
Vancomycin	In neonate: 45 mg/kg/day in divided doses every 8 hours. In children: 60 mg/kg/day in divided doses every 6 hours.
Benzyl penicillin	In neonate: 100,000 units/kg/day in divided doses every 6–12 hours according to the age. In children: 400,000 units/kg/day in divided doses every 4–6 hours.
Chlor-amphenicol	100 mg/kg/day IV in divided doses every 6 hours (max dose 4 g/day).

Table 14.7: Drugs of choice according to the culture isolates.

Organisms	**Drugs of choice**
E. coli	Cefotaxime Ceftriaxone, Gentamicin
Group B streptococcus	Benzyl penicillin
Listeria monocytogenes	Ampicillin
Pseudomonas	Ceftazidime
H. influenzae	Cefotaxime Chloramphenicol Ceftriaxone
N. meningitides	Benzyl penicillin Ceftriaxone
S. pneumonia	Vancomycin Benzyl penicillin Ceftriaxone
Staph. aureus	Ceftazidime Vancomycin

Treatment of complications

Cerebral edema and raised ICP

- Head is elevated about 30°
- Steroids decrease the meningeal inflammation and brain water content and so decrease ICP
- Mannitol is also given

Subdural effusions

- In the presence of increased intracranial pressure or a depressed level of consciousness, a symptomatic subdural effusion should be aspirated.

Inappropriate ADH secretion

- There is hyponatremia (Na^+<130 mEq/l), coma, seizures, weight gain, puffiness of face, decreased urine output, and high urinary specific gravity.
- It is treated with fluid restriction and diuretics.

Shock (Waterhouse Friderichsen syndrome)

- Patient is in shock with hypotension and petechial rash (a complication of meningococcemia).
- It is treated with normal saline or plasma, steroids and dopamine infusion.

Table 14.8: Recommendations for repeat LP at 24–36 hours.

- All neonates
- Meningitis caused by resistant S. pneumonia
- Meningitis caused by Gram-negative enteric bacilli
- Lack of clinical improvement in 24–36 hours after start of therapy
- Prolonged or second fever
- Recurrent meningitis
- Immunocompromised host

Complications of meningitis

- Increased Intracranial Pressure (ICP)
- Cranial nerve palsies
- Seizures
- Stroke
- Ataxia
- Inappropriate ADH secretion: It leads to hyponatremia, and cerebral edema.
- Prolonged fever (>10 days): It may be due to intercurrent viral infection, a secondary or nosocomial bacterial infection, drug reaction or thrombophlebitis.
- Rapidly increasing head circumference: It suggests hydrocephalus due to inflammatory obstruction of CSF pathways. Cranial USG or CT scan can differentiate it from subdural effusion.
- Subdural effusions: Noted in 50% of the patients during the acute illness. It is more common in infants. Subdural effusion may be associated with a rapidly increasing head circumference, abnormal transillumination test, vomiting, seizures, full fontanel, focal neurologic signs, or persistent fever.
- Spastic paraparesis: Meningomyelitis and spinal cord infarction may cause spastic paraparesis with or without sensory loss.
- Blindness: Optic nerve arachnoiditis may lead to optic atrophy and eventual blindness.
- Cerebral infarcts are diagnosed by CT scan within 1–2 days of onset of febrile illness.
- Anemia is more common in *H. influenzae* meningitis and is due to hemolysis, DIC or bone marrow suppression.
- Cerebral or cerebellar herniation
- Long term neurologic abnormality. (Mental retardation, hemiplegia)
- Epilepsy
- Deafness
- Spasticity
- Visual handicap or squint
- Repeated episodes of meningitis

There are three types of repeated episodes of meningitis:

- **Recrudescence:** Reappearance of infection during therapy with appropriate antibiotics.
- **Relapse:** It occurs between 3 days and 3 weeks after therapy and represents persistent bacterial infection in the CNS (subdural effusion, cerebral abscess, ventriculitis) or some other site (mastoiditis, orbital infection, cranial osteomyelitis or cellulitis).
- **Recurrence:** A new episode of meningitis due to re-infection with the same bacterial species or another pyogenic pathogen.

Duration of antibiotic therapy

- Treatment for uncomplicated penicillin-sensitive *S. pneumonia* meningitis should be for 10–14 days with a third-generation cephalosporin or intravenous penicillin. If the isolate is resistant to penicillin and the third-generation cephalosporin, therapy should be completed with vancomycin.
- Intravenous penicillin for 5–7 days is the treatment of choice for uncomplicated *N. meningitidis* meningitis.
- Uncomplicated *H. influenzae* type b meningitis should be treated for 7–10 days.
- Patients with partially treated meningitis and who do not have an identifiable pathogen should continue to receive therapy with ceftriaxone or cefotaxime for 7–10 days.
- Gram-negative bacillary meningitis should be treated for 3 weeks or for at least 2 weeks after CSF sterilization, which may occur after 2–10 days of treatment.

Prognosis

- Prognosis depends on many factors:
  - Patient's age at the onset of meningitis (young age)
  - The duration of the disease before appropriate antibiotic therapy was started
  - The specific microorganisms involved
  - The number of organisms or quantity of capsular polysaccharide antigen in CSF
  - Disorders that compromise host response to infection
  - The presence of focal neurologic findings (not postictal) at admission

  - Late-onset seizures
  - Coma at presentation
  - Shock
  - Low or absent CSF white blood cell count in the presence of positive Gram stain of the CSF
  - Presence of inappropriate ADH secretion
  - Immunocompromised condition
- The worse prognosis is in young children with higher bacterial colony counts (10^7 organisms grow in CSF), intractable seizures, subdural effusion, bacteremia, and prolonged fever.
- Especially in meningococcal meningitis, the poor prognostic signs are:
  - Development of hypotension or coma
  - Rapidly progressive purpura within 12 hours
  - Disseminated Intravascular Coagulation (DIC)
  - Absence of meningitis in the presence of meningococcemia
  - Absence of leukocytosis
  - Thrombocytopenia
  - Low ESR.

CASE

Meningococcemia: A 3-year-old boy presents with ***high grade fever***, rigors and chills for last 2 days. Now, he has developed ***purpuric rash*** on feet and is becoming ***unconscious***.

- Mortality rate is 25% in pneumococcal, 15% meningococcal and 8% in *H. influenzae* meningitis.
- 35% of survivors have permanent deficit e.g. deafness, learning disabilities, blindness, seizures, or hydrocephalus. These are more common in pneumococcal meningitis.
- Survival for 2 days following initiation of therapy is a good prognostic sign in meningococcal infection.
- All patients with bacterial meningitis should be assessed for hearing or vision deficit before discharge from the hospital.

Prevention

Vaccination

- Vaccines are available for immunization against *S. pneumonia*, *N. meningitides* (A, C, Y, W135), and *H. influenzae type b*.
- Pneumococcal polysaccharide vaccine is a 23-valent vaccine. It is effective in children older than 17 months. Vaccine is recommended for children at high risk for pneumococcal infection (e.g. functional or anatomical asplenia, nephrotic syndrome, etc). Dose is 0.5 ml IM single dose.
- The meningococcal vaccine is recommended for high-risk group and children with defects of the terminal component of the complement cascade (C5–C9). It is a quadrivalent vaccine (A, C, Y, and W135).
- *H. influenzae* vaccine is given for all infants above 2 months of age.

Antibiotic prophylaxis

Meningococcal prophylaxis

- The dose of rifampicin recommended for meningococcal prophylaxis is 10 mg/kg (maximum 600 mg) given every 12 hours for 2 days.
- Contact is defined as a person who has direct exposure to secretions e.g. mouth-to-mouth resuscitation, suctioning, or intubation.

H. influenzae prophylaxis

- The dose of rifampicin recommended for H. influenzae prophylaxis is 20 mg/kg/day (maximum 600 mg) given once daily for 4 days.
- Rifampicin prophylaxis is recommended for all household contacts (including adults) if an unvaccinated child younger than 4 years of age lives in the home.
- A household contact is defined as a person who lives in the residence of the index case or who has spent a minimum of 4 hours with the index case for at least 5–7 days before patient's hospitalization.
- Patient should also receive the same dose of rifampicin before discharge from the hospital to prevent reinfection because 10 days' treatment of meningitis cannot eradicate the nasopharyngeal colonization of H. influenzae type b.

Streptococcus pneumonia prophylaxis

- Routinely, no chemoprophylaxis is recommended.

TUBERCULOUS MENINGITIS

CASE

A 12-year-old child presents with ***fever*** and loss of appetite for ***two months***. He is irritable and in altered sensorium since 7 days. He has history of ***headache***, photophobia, nausea, vomiting, and neck pain. On examination, patient is pale, febrile with toxic look, ***disoriented*** with Glasgow coma scale 12/15. He has ***signs of meningeal irritation***. Investigations show elevated ESR. Chest X-ray shows bilateral diffuse milliary infiltrates. CSF analysis reveals ***low sugar*** (29 mg/dL), ***raised protein*** (164 mg/dL), cell count 32 cells/mm^3 ***predominantly lymphocytes***. His cranial MRI shows mildly dilated ventricles and hyperintense lesions suggestive of TBM.

Definition

- It is inflammation of the leptomenings (pia–arachnoid) by Mycobacterium tuberculosis.

Incidence

- Involvement of the Central Nervous System (CNS) is the most serious complication of tuberculosis.
- TBM complicates 1 of every 300 primary infections.
- It is not reported in infants below 4 months of age because pathologic events take at least 4 months to develop.
- The maximum risk of TBM is within 6 months of primary infection.
- The highest incidence is recorded below 5 years of age.

Pathogenesis

- Tuberculous meningitis is always a secondary lesion with primary usually in the lungs.
- Meningitis results from the formation of a metastatic caseous lesion (seeding of the bacilli) in the cerebral cortex, meninges and choroid plexus during the process of initial occult lymphohematogenous spread of the primary infection.
- Within a short period of time, caseous foci form on the surface of brain (Rich's foci). They increase in size and discharge bacilli in the CSF (subarachnoid space).
- A thick, gelatinous exudate may infiltrate the cortical or meningeal blood vessels, producing inflammation, obstruction, or infarction. Most commonly involved site is the brain stem causing frequent involvement of 3rd, 6th, and 7th cranial nerves.
- Basal cisterns are obstructed causing communicating hydrocephalus. Accompanying inflammation may cause cerebral edema.

Clinical findings

- In a classical case, onset is insidious but may be fulminant in certain cases.
- A more rapid progression of the disease may occur in young infants in whom symptoms develop for only several days before the onset of acute hydrocephalus, brain infarction, or seizures.
- Classically, the onset is gradual (over several weeks).
- History of measles may precede the onset of TBM.
- The clinical manifestations may be divided into 3 stages and each stage lasts approximately 1 week. There may be considerable overlap of the 3 stages.

Stage 1 (prodromal stage): (lasts for 1–2 weeks)

- Initial symptoms are nonspecific.
- The child becomes listless or irritable, loses interest in play, have fever, anorexia, vomiting, constipation and weight loss.
- Some children may complain of headache and drowsiness.
- There are no focal neurologic signs.
- There may be loss of or stagnation of the developmental milestones.

Stage 2

- Onset of 2nd stage is more abrupt.
- During this stage signs of meningeal irritation (neck stiffness) appear with increased CSF pressure. Positive Kerning and Brudzinski signs develop with increased tendon jerks and extensor plantar responses. There may be generalized hypertonia.
- Headache is the cardinal symptom in the 2nd week of illness in older children. Fever is constant and headache is severe, persistent and often occipital.
- Vomiting and constipation may become severe.
- Exudate develops at the base of brain involving cranial nerves and brain stem.
- Abducent nerve paralysis is common. Oculomotor lesion causes internal squint. Facial palsy is also common.
- Some children may have disorientation, and speech and movement disorders.
- In infants anterior fontanel may be bulging and sutures become separated with "crackpot" sign.
- In older children papilledema develops. Head circumference starts enlarging rapidly.
- Choroid tubercles may be seen.
- Child is semiconscious and may shriek loud noises and develops convulsions.
- All the above clinical features are due to the development of hydrocephalus and increased intracanial pressure along with meningeal irritation.

Stage 3

- Child rapidly becomes comatose during 3rd week.
- He is emaciated with scybalous masses in the abdomen.
- Child starts getting high-grade irregular fever and convulsions.
- There may be hemiplegia or paraplegia.
- With extreme neck stiffness opisthotonus develops with decerebrate rigidity and pupil becomes dilated and fixed.
- There is deterioration of the vital signs especially hypertension.
- Death may occur if treatment is started late during this stage.
- Tache-cerebrale is sometimes seen in children. The response is elicited by stroking of the skin with a blunt instrument. In 30–60 seconds it produces an erythematous, raised reaction, which lasts several minutes.

Diagnosis

Clinical suspicion

- A high index of clinical suspicion is important where tuberculosis is common (history of contact).
- Tuberculin skin test is negative in 50% of the patients.
- Chest X-ray may be normal in 20–50% of the patients.

Blood

- ESR is high.

- Total and differential leukocyte count reveals normal count with predominant lymphocytosis.

X-Ray chest

- Usually there is some evidence of tuberculosis in the lungs, hilar adenopathy, and patch of pneumonia or miliary tuberculosis.

Lumbar puncture (CSF examination)

- CSF pressure increased.
- Color is clear hazy or straw colored.
- Cobweb is formed when left for over 12 hours.
- Protein is markedly raised (400–5,000 mg/dl). It is raised because of hydrocephalus and spinal block.
- Glucose is decreased (below 40 mg/dl). It rarely goes below 20 mg/dl as is seen in pyogenic meningitis.
- Pleocytosis with predominant lymphocytes (10–500/mm^3). Early evaluation may reveal a predominance of polymorphonuclear leukocytes, but in most cases, lymphocytes predominate.
- Smear and culture: Ziehl-Neelson stain may reveal acid-fast bacilli. CSF culture or guinea pig inoculation will confirm the diagnosis.
- Mycodot: Antigen detection by polymerase chain reaction

Gastric lavage or **sputum examination** for tubercle bacilli

Lymph node biopsy in certain cases to confirm the diagnosis

Fundoscopy (tubercles, papilledema or optic atrophy)

CT Scan

- It may help establish a diagnosis of tuberculous meningitis. It also aids in evaluating the success of therapy. There may be:
    - Brain stem meningitis (basilar enhancement)
    - Hydrocephalus
    - Focal infarcts
    - Tuberculomas
- CT scan may be normal during the early stages of the TBM.

Management

Specific treatment

- Most patients are hospitalized at the beginning of treatment but receive most of prolonged drug course as out patients.
- Start treatment with 4 anti-tuberculous drugs and treatment should be continued for 12 months.

Isoniazid (INH)

- It is the drug of first choice.
- It is rapidly absorbed and penetrates readily into the CSF.
- Isoniazid and rifampicin are highly bactericidal for M. tuberculosis.
- It is excreted through the kidney.
- Dose is 10–15 mg/kg/day.
- Main side effects are hepatotoxicity, peripheral neuropathy, optic neuritis, hypersensitivity and fever. Peripheral neuritis is due to competitive inhibition of pyridoxine.
- Transient elevation of aminotransferases (up to three times normal) may be seen at 6–12 weeks, but therapy is continued unless clinical illness occurs.

Rifampicin

- It is also a first line drug, well absorbed and penetrates CSF well.
- Dose is 10–20 mg/kg/day one hour before breakfast.
- It causes orange discoloration of the urine and tears, GIT disturbances, and hepato-toxicity.
- Combined use of INH and rifampicin increases the risk of hepatotoxicity, which can be decreased by lowering the dose of INH (10 mg/kg/day).

Pyrazinamide

- It is bactericidal in acid medium and enters CSF readily.
- It is used as a third drug for 2–3 months initially.
- Dose is 30 mg/kg/day.
- Main side effects are arthralgia, arthritis, hyperuricemia (gout).

Streptomycin

- It is bactericidal for extracellular tubercle bacilli, but its penetration into macrophages is poor.
- Its penetrance into CSF through inflamed meninges is excellent but do not cross the un-inflamed meninges.
- Dose 20–40 mg/kg/day given I/M for 2 months.
- Side effects are ototoxicity (vestibular or hearing loss) nephrotoxicity and may cause hypersensitivity reactions.

Ethambutol

- It is used as an alternate drug to rifampicin.
- It is not recommended below 6 years of age.
- Dose 15–25 mg/kg once daily.
- Side effects are optic neuritis, hypersensitivity and GIT upsets.

General measures

- Corticosteroids:
    - Steroids decrease mortality rate and long-term neurologic sequelae.
    - They reduce vasculitis, inflammation, and intracranial pressure.
    - Dose of prednisolone is 1–2 mg/kg/day for 6–8 weeks.
    - If initially given IV, dose of dexamethasone (Decadron) injection is 0.2 mg/kg/IV.
    - It helps to reduce cerebral edema and prevents formation of adhesions.
- Careful record of vital signs.
- Daily monitoring of the complications is also very important for early recognition and proper treatment

of the complications. Main complications to be monitored are:
  - Raised intracranial pressure
  - Syndrome of inappropriate ADH secretion
  - Drug toxicity, etc.
- Phenobarbitone: Dose 5 mg/kg/day to control convulsions.
- Antipyretics: Paracetamol (65 mg/kg/day) and fresh water sponging to control temperature.
- Pyridoxine 10 mg daily to prevent polyneuritis. Pyridoxine administration is not generally recommended in children with adequate diet. It is indicated in children with inadequate diets, and in breastfed babies.
- Feeding: Give tube feeding according to the requirement. Ideally, 100 calories/kg/day are given which should contain 2 g/kg/day protein to prevent catabolism. Iron and multivitamin supplements may be needed in a previously malnourished child to prevent further malnutrition.
- Bed Sores: Change posture every two hours to prevent bedsores.
- Care of comatose patient
- Care of bowel and bladder
- It is also important to screen the family members for tuberculosis and treat the infected persons.

Complications

- Mental retardation
- Cranial nerve palsies (3rd, 6th, and 7th)
- Blindness (optic atrophy)
- Deafness
- Hydrocephalus
- Hemiplegia, paraplegia, or monoplegia
- Epilepsy
- Endocrine disturbances (diabetes insipidus)
- Tuberculoma

Prognosis

- It depends upon two factors:
  - Age of the patient.
  - Stage of the disease at which treatment is started.
- Without treatment it is invariably fatal.
- In stage I, 100% cure rate is expected.
- Even with optimal therapy mortality ranges from 30–50% and incidence of neurologic sequelae is 75–80% especially in stage 3. There may be blindness, *deafness, paraplegia, mental retardation, and diabetes* insipidus.
- Infants and young children have poor prognosis as compared to older children.

ENCEPHALITIS

CASE

Herpes encephalitis: A 6-year-old boy presents with ***fever*** and lethargy. He develops focal ***fits***. An EEG shows periodic ***complexes over the temporal area***. The result of CSF is WBC 55 cells/mm^3, neutrophils 60%, ***RBC 2100/mm^3***, protein 3.2 g/l, glucose normal. On microscopy, ***no organisms*** are seen.

Definition

- The inflammation of the brain tissue is known as encephalitis.
- Encephalitis results in marked cerebral dysfunction and early loss of consciousness.
- It is usually caused by viruses e.g. influenza, herpes simplex but brain tissue is also involved as part of bacterial meningitis (e.g. tuberculous meningoencephalitis, etc.)
- Sometimes features of encephalitis occur after few days of known viral infection or vaccination and it is then called **"Parainfectious" encephalitis.**
- Neurologic manifestations suggestive of encephalitis but occurring in the absence of inflammation indicate encephalopathy.
- Patient is only labeled as encephalitic when known metabolic and toxic causes of encephalopathy (Reye's syndrome, hepatic encephalopathy, hypertensive encephalo-pathy, diabetic ketoacidosis, or lead encephalopathy) have been ruled out.

Etiology

- Encephalitis is mainly caused by viruses but in cases where viruses have not been isolated, etiology is presumed to be viral.
- It is caused by direct viral infection of the brain via a hematogenous or neuronal route.
- Arboviruses and enteroviruses are most commonly responsible for epidemics of acute encephalitis.

Table 14.9: Causes of viral meningitis/encephalitis

Infections	Postinfectious
• Coxsackie • Poliomyelitis • Echo-virus • Mumps • *Rabies* • Herpes simplex • Herpes zoster • Yellow fever • Dengue fever	• Measles • Rubella • Varicella • Pox virus • Vaccinia

- Herpes simplex is the most common cause of sporadic encephalitis.
- Varicella virus commonly causes cerebellar ataxia.

Pathophysiology

- Following ingestion or mosquito bite, the virus infects several organs, where it multiples causing a systemic febrile illness.
- CNS is involved in the secondary viremia if the virus continues to multiply in the primary organs.
- The neurologic damage occurs either by:
    - Direct invasion and destruction of neural tissues by actively multiplying viruses
    - Reaction of the patient's tissue to antigens of the virus
- The brain is swollen with marked vascular congestion, and initial polymorph response is followed by mononuclear, lymphocyte and plasma cells infiltration.
- There is degeneration of the neuronal cells and intranuclear inclusion bodies may be present.
- Certain viruses appear to have an affinity for invading certain parts of the brain e.g. herpes simplex for fronto-temporal lobe; mumps virus is often associated with transverse myelitis; chickenpox for cerebellum.

Clinical findings

- All viruses, which cause encephalitis, can also cause meningitis. Encephalitic picture may predominate or a combined picture of meningo-encephalitis may occur if meninges are also inflamed.
- The clinical features are extremely variable. A sudden onset of high fever and headache are the first signs of the illness.
- Signs of central nervous system involvement occur early which vary from mild drowsiness to deep coma.
- Headache, fever, irritability, mental confusion or abnormal behavior may be marked. Headache is common in older children whereas infant may have gross irritability and feeding difficulty.
- Focal neurological signs may occur; cranial nerve palsies (squint or facial palsy), speech disturbances (aphasia), spastic palsies (hemiplegia, tetraplegia), cerebellar disturbances (ataxia) and abnormalities or various reflexes.
- Meningeal inflammation may produce neck rigidity and stiffness of back.
- Some children may present with abnormal behavior screaming spells, irritability, confusion, tremors and stupor.
- Muscle weakness and occasionally paralysis may occur.
- Spastic paraplegia with loss of bowel and bladder control indicates spinal cord involvement.
- Sensory disturbances may be present in some.
- Respiratory irregularities and visual disturbances may occur.

Table 14.10: Features of encephalitis.

Features of encephalitis

Most common causes:	Clinical features:
• Herpes • Measles • Chicken pox • Polio	• Fever • Disturbed consciousness • Convulsions • Focal neurologic signs

Encephalitis: Direct invasion of gray matter by infectious agents.

Postinfectious: Delayed immunologically mediated demyelination.

Encephalopathy: Encephalitis like illness without fever or aseptic meningitis (inflammation) is called encephalopathy and is due to toxic or metabolic causes.

- Occasionally myocarditis and hypotension may complicate the picture.
- The clinical features usually do not point to a specific viral etiology but some types of encephalitis present distinct clinical features e.g. Herpes simplex; since it is treatable.

Herpes simplex encephalitis

Type 1

- Infants and children typically present with fever, vomiting, and lethargy and proceed to coma and focal fits.
- It usually produces features of a space-occupying lesion in the temporal lobe like hemiparesis, focal fits and raised intracranial pressure.
- Tentorial herniation, papilledema and decerebrate posturing may occur.
- CSF examination may show xanthochromia and in some cases RBCs. Cell count varies from 50–5000, CSF protein is normal or moderately elevated with normal glucose.

Type 2

- Herpes virus type 2 causes encephalitis in the newborn following vaginal delivery.
- Virus is acquired from maternal birth canal and results in typical vesicular skin eruptions and encephalitis.

Chickenpox encephalitis

- Occurs 4–6 days after the rash but it can precede the rash in some.
- CSF shows 10–15 cells/mm^3 with polys initially and lymphos later. Protein is normal or moderately elevated with normal glucose.

Measles encephalitis

- It usually develops 2 days to 2 weeks after the appearance of rash, rarely even before.
- Spinal cord involvement with paraplegia and neurologic bladder may occur with inappropriate ADH secretion.
- CSF reveals lymphocytic pleocytosis of 50–250 cells with slightly raised protein and normal glucose.

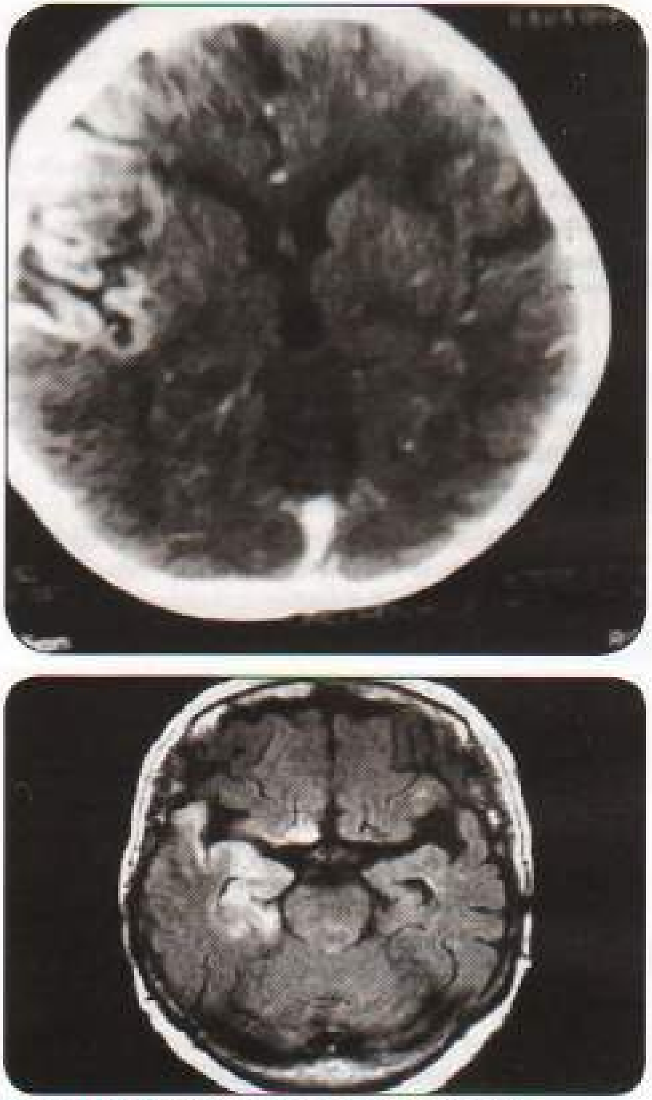


Figure 14.4: Showing temporal lobe involvement.

Polio encephalitis

- Occurs in 1–5 percent of patients showing neurological manifestation of polio infection.
- Drowsiness, irritability, coarse tremors, coma and fits indicate encephalitis in addition to the usual symptoms of paresis of limbs or brain stem involvement.
- Although sensory deficits are rare but these can occur in the presence of transverse myelitis or following involvement of the posterior horns of the gray matter.
- CSF shows mild pleocytosis of 50–200 cells, initially polys and later lymphos. Protein in CSF is moderately elevated and glucose normal.
- Polio-encephalitis should always be considered in differential diagnosis, as it is common here.

Mumps

- Mumps is commonly associated with aseptic meningitis, which occurs 2–3 days after the onset of parotitis, but encephalitis occurs 7–10 days later with frequent convulsions and coma.

- Diagnosis is confirmed by virus isolation, serological methods and fluorescent antibody techniques.

Slow viral diseases

- Slow viral diseases are manifested months to years after the viral infection.
- Slow CNS infection is due to prions (small proteinaceous particles).
- There is dementia, poor cognitive functions, and behavior changes.
- Most common viruses causing such type of disease are measles (Subacute Sclerosing Panencephalitis or SSPE), rubella, HIV and HSV.

Diagnosis

- Diagnosis is essentially clinical and by exclusion of diseases such as meningitis, cerebral malaria, brain tumor, heat stroke and lead encephalopathy.
- History of:
  - Exposure to specific illness such as measles, polio and chickenpox in past 2–3 weeks
  - Exposure to mosquitoes, ticks and animals
  - Recent injections specially vaccination (Pertussis)
  - Exposure to heavy metals or pesticides

Lumbar puncture

- Cerebrospinal fluid should be examined to exclude bacterial and tuberculous meningitis.
- In viral encephalitis CSF is generally clear; leukocyte count varies from 10–5000 cells with polymorph initially and lymphocytes later. There is moderate elevation of protein with normal glucose.

Antibody titer

- Serologic testing should be done twice 15 days apart to demonstrate rising titer (4 fold or more).

Virus isolation

- Viruses can be isolated from blood, CSF, feces and throat swabs.

Brain scan and CT scan

- These are helpful in localizing the process as in focal necrotizing encephalitis (herpes simplex).

Brain biopsy

- The diagnosis is established and confirmed by brain biopsy.
- It is only indicated in cases, which are suspected to be having herpes encephalitis because specific antiviral chemotherapy is available.
- Virus is then identified by immunofluorescent technique from brain biopsy.

EEG

- Infection of the brain causes very marked disorganization of the EEG with the development of large amplitude, slow waves.

- In herpes encephalitis there are large amplitude, slow waves at rate of 2–4/sec and these waves recur after every 2 sec on a background of very slow activity in the temporal region.

Blood counts

- These are done to rule out bacterial infections.

Complications

Early

- Hemiplegia
- Squints
- Deafness
- Intractable convulsions
- Bed sores
- Aspiration pneumonia
- Urinary tract infection from catheterization

Late

- Mental retardation
- Hydrocephalus
- Epilepsy
- Learning disabilities
- Behavior disorders

Management

Nursing care

- Nursing a comatose child is a skillful act and requires monitoring vital functions, frequent suctioning of airways, change of posture every ½-1 hour to avoid pressure sores and positional deformity.
- Attention should be paid to oral hygiene, eye care, and abdominal distension from bladder enlargement (urinary retention) and bowel care (ileus or severe constipation).

Anticonvulsants

- Injection diazepam 0.2 mg/kg I/V or injection paraldehyde 0.15 ml/kg per rectal.
- Once convulsions are controlled give phenobarbitone 5–8 mg/kg/day orally to prevent further convulsions.

Cerebral edema

- Raised intracranial pressure and cerebral edema is present in most cases even without any evidence of papilledema and should be treated.
- Dexamethasone injection is given in a dose of 0.5 mg/kg/day for few days to reduce cerebral edema and then dose is tapered with oral dexamethasone.
- Mannitol as 20% solution in a dose of 10 ml/kg/day in ½-1 hour: May be repeated every 8–12 hours.

Antiviral drugs

- For herpes simplex virus infections, acyclovir is the treatment of choice.

Intravenous fluids

- Maintain fluid and electrolyte balance.
- Fluids should be restricted to 60% of the daily requirement and do not give dextrose water or 0.18% saline which results in cerebral edema.

Nutrition

- Calories required are given through nasogastric tube in the form of liquid and semisolid diets e.g. milk, juices, soup, egg, etc.

Antibiotics

- Antibiotics should be given until bacterial etiology is ruled out by blood and CSF examination.

Antipyretics

- High fever should be controlled by antipyretics or tepid sponging.

Maintenance of airway

- Maintenance of airway is extremely important in an unconscious patient and equipment for artificial respiration should be at hand.

Prognosis

- Most patients survive and some may have residual focal defects.
- Mortality varies from 10–50%.
- The outcome is particularly poor in herpes simplex encephalitis (mortality rate >70%) while better in enteroviral encephalitis.
- Encephalitis is usually severe in children <1 year of age and in those presenting with coma.

CEREBRAL MALARIA

CASE

A 5-year-old child presents with ***high grade fever*** for 3 days and generalized tonic clonic ***seizures*** for 1 day. On examination, he is pale, ***comatose*** and has mild ***jaundice***. Liver is palpable 2 cm below right costal margin. Spleen is palpable 3 cm below left costal margin (***hepatosplenomegaly***). There are fundal hemorrhages.

Definition

- It is a severe form of malaria caused by *Plasmodium falciparum*, manifesting as coma, convulsions and/or hemoglobinuria.

Etiology

- *Plasmodium falciparum* is transmitted from:
    - Bites of previously infected female *anopheles* mosquitoes
    - Transfusion of infected blood
    - Organ transplant and by hypodermic needles

Epidemiology

- The infection is usually much more severe in young children. This is because the number of parasites in children and adults are the same but the children have a proportionately smaller size.

- A and B blood groups are more protective than O groups.
- Hemoglobin E and C are also more protective.
- Fetal hemoglobin, sickle cell trait and G6PD deficiency have lesser tendency of *Plasmodium falciparum* infection.
- Malnutrition is protective as immunity is decreased.

Pathophysiology

- First the *Plasmodium falciparum* enters the red blood cells.
- After 8–18 hours, these cells become increasingly sticky and tend to adhere to the endothelial lining of blood sinuses and vessels especially when the circulation is slow. The fixed cells are unable to come back to the general circulation.
- As more cells adhere, flow within the vessels is progressively impeded and occlusion or even rupture may occur.
- The symptoms depend on the site and extent of the occlusion of the blood vessels. The lungs, brain and intestinal tract are usually more affected.
- The parasites keep maturing in the infected cells even when they are fixed to the endothelium or sinuses.
- The release of merozoites, where the circulation is slowed, facilitates the invasion of nearby red blood cells.
- *Plasmodium falciparum* invades all erythrocytes irrespective of age and so parasitemia in a non-immune child may be very heavy.
- One schizont yields 8–32 merozoites, the highest of all the species.
- Its incubation period is 10–13 days.

Pathology

- When the parasitized red blood cells attach to the endothelium of venules and capillaries, the inflammatory process starts around them. There is hemorrhage and necrosis around these vessels.
- All these lead to the blockage of vessels by parasitized red blood cells. Fibrin thrombi may also form in the arterioles and capillaries giving a picture of DIC. The same process in the brain leads to the cerebral edema.
- The immunoflourescence has shown the deposition of *Plasmodium falciparum* antigen and antibody complex in capillaries. There are two suggested ways to explain:
  - ICAM (Intercellular Adhesion Molecule) mediated increased adherence of RBC's to the endothelium of cerebral vessels.
  - NO (Nitric Oxide) mediated increased fragility and destruction of cerebral matter.

Clinical findings

- The characteristic adult pattern of cerebral malaria is not present in children, especially under 5 years of age.
- The clinical signs and symptoms usually start after 8–15 days of infection. Initially there are behavior changes like anorexia, fretfulness, unusual crying, drowsiness, or disturbance of sleep.
- Fever may be absent or increase gradually for 1–2 days or the onset may be sudden with high-grade temperature with or without prodromal chill.
- The complaints include headache, nausea, generalized aching, particularly of the back.
- When the spleen has enlarged quickly and is tender, there can be pain in the abdomen.
- Cerebral symptoms are evidenced by convulsions or coma. The neurologic signs in infants and children are those of increased intracranial pressure and symmetric upper motor neuron and brainstem disturbances such as disconjugate gaze and decerebrate and decorticate postures.
- There is severe pallor and splenomegaly (or hepatosplenomegaly; liver may only be enlarged at times).
- The classic picture of a child with high-grade fever who is unconscious and convulsing cannot be mistaken.
- There is no neck rigidity (except abnormal posturing).

Diagnosis

- CBC:
  - Leucopenia is variable
  - Monocytosis is common
  - Anemia
  - Reticulocyte count increased
- Thick and thin blood film: (Most specific test)
  - Initially ring forms are seen and after 10 days crescents (gametocytes) are seen.
  - Up to 20% of RBC's may be infected.
  - Negative if antimalarials are given.
- CSF:
  - Usually normal if no associated meningitis
- Serum electrolytes
- Blood sugar: Hypoglycemia
- Detection of parasitic antigen:
  - ICT–Malaria
  - DNA/RNA are detected with probes
- Serological tests: Not very specific but species specific antibodies can be detected.

Management

Supportive treatment

Anemia

- Give blood transfusion if hemoglobin <6 gm %. (Pack cells 10 ml/kg).

Hypoglycemia

- Give 50% glucose bolus I/V stat and then regular glucose supplements with 10% dextrose water.

Renal failure

- Increase hydration
- May require dialysis
- Decrease the dose of anti-malarial to 1/3

Convulsions

- Diazepam 2.5–5.0 mg IV slow
- Phenobarbitone (10 mg/kg PO/NG tube stat, then maintenance dose 5 mg/kg/day in 2 divided doses)
- Paraldehyde (0.15 ml/kg P/R)

Lowering of high temperature

- Tepid sponging or paracetamol orally by N/G tube

Fluids

- 5% dextrose saline 20–40 ml/kg in 30 minutes or dextran 75%
- Later shift to 5% dextrose 1/5 saline
- Total fluid 100–150 ml/kg/day

Specific treatment

- Start IV anti-malarials and then shift to oral when the patient becomes conscious.
- **Injection quinine dihydrochloride:** (300 mg/1 ml vial): 20 mg/kg IV stat, then 10 mg/kg IV–8 hourly for 7 days (1 mg in 1 ml of 5% dextrose water over 2–4 hour).
- 8.3 mg quinine base = 10 mg quinine dihydrochloride
- **Injection chloroquin dihydrochloride:** (200 mg/5 ml vial): 5 mg/kg in 10 ml/kg of isotonic saline in 3–4 hours, then repeat same dose at 6 hours. Then give 5 mg/kg daily for 3 days.
- **Quinine sulphate:** 10 mg/kg/dose–8 hourly for 4–7 days PO.
- **Chloroquin phosphate/hydrochloroquin sulphate:** 10 mg/kg stat. Then 10 mg/kg next day.Then 5 mg/kg next day.
- **Injection artemethrine:** It is also in use these days. Dose 3.2 mg/kg IM stat then 1.6 mg/kg/day for 2 days.

Differential diagnosis

- **Febrile fits:** Age 6 months–6 yr, patient is rousable, CSF clear.
- **Pyogenic meningitis:** Toxic ill patient. Signs of meningeal irritation positive. CSF is turbid and abnormal.
- **Viral encephalitis:** Anemia, coagulopathy and malarial parasite is absent. CSF may be normal with increased proteins and pleocytosis.
- **SOL:** Increased ICP evidenced by vomiting, headache, diplopia and papill-edema. Localizing signs and cranial nerve palsies are present. Malarial parasite is absent. MRI/CT scan confirm.
- **Hepatic coma:** Deep jaundice and less anemia. Liver is usually smaller. LFT's gross abnormality.Coagulation defects.Decreased serum proteins and especially serum albumin. Malarial parasite is negative.
- **Hypoglycemic coma:** Afebrile, cold and sweating. Jaundice, anemia, bleeding and MP are absent. Serum sugar is <40 mg %.
- **Uremia:** H/O preceding edema, diarrhea, and vomiting. Hematuria, dysuria and recurrent abdominal pain.H/O previous UTI or renal stones.

Criteria for cerebral malaria diagnosis

CNS

- Unarousable or coma >6 hours
- Focal or generalized fits
- Posture (opisthotonic, decerebrate, decorticate)
- Conjugate deviation of the eyes
- Retinal hemorrhages

Renal

- Urine output <400 ml/day
- Serum creatinine >3 mg%

Prognosis

- Mortality of cerebral malaria ranges from 10–30%.
- Death in most of the cases occur within 24 hours of admission/treatment.
- Some children have a rapid and progressive recovery, but most of the time duration of impaired consciousness after treatment being started ranges from few hours to several days.
- Majority of the surviving children had a full recovery but about 10% have a permanent neurologic deficit.

FEBRILE CONVULSIONS

CASE

An 18-month-old child is ***otherwise normal***. This morning, he has a brief, ***generalized, self-limited seizure*** associated with ***high temperature***. Physical examination is normal. He had ***completely recovered*** within 1 to 2 hours of the seizure when fever subsided.

Definition

- Febrile convulsions are defined as seizures associated with fever in the absence of detectable CNS infection.
- These are generalized tonic/clonic seizures with loss of consciousness in otherwise healthy children.

Criteria for febrile seizures

- Age of 3 months to 5 years. Most febrile seizures occur between the ages of 6–18 months
- Fever of 38.8°C
- Non-central nervous system infection

Exclusion to the diagnosis

- A history of previous afebrile seizures
- CNS infection or inflammation
- Acute systemic metabolic abnormality causing convulsions

Incidence

- These are most common causes of childhood convulsive disorder and occur in 3–4% of children.
- These are twice as common in boys as girls.

General considerations

- More than 90% febrile seizures are:
  - Generalized
  - Less than 5 minutes duration
  - Occur early in an illness (e.g. otitis media, pharyngitis, adenitis, or UTI)
- A strong family history of febrile convulsions in siblings and parents suggests a genetic predisposition. An autosomal dominant pattern of inheritance may be present.
- 2–4% febrile seizures lead to epilepsy or recurrent non-febrile seizures.
- Chance of later epilepsy is higher in complex febrile seizures. Other factors leading to epilepsy are:
  - An abnormal neurologic status before the occurrence of seizures (e.g. cerebral palsy, mental retardation).
  - Early onset of febrile seizures (i.e. before 1 year of age)
  - A family history of epilepsy
- In the presence of above factors, risk of epilepsy after febrile seizures is 15–20%. Recurrent febrile seizures occur in 20–40% of cases.
- Meningitis should be ruled out even in a child who has previous history of febrile seizures. The younger the child, the more important is the CSF examination because physical findings are not reliable to diagnose meningitis.
- Indications for CSF examination in a case of febrile seizures are:
  - If the child is under 1.5 years of age
  - If recovery is slow
  - If no other cause of the fever is found
  - If close follow-up is not possible

Etiology

- Rapid increase in body temperature has been postulated but exact pathogenesis is unknown.
- Viral rather than bacterial infections cause disturbance of cerebral electrical activity.

Clinical findings

- Febrile convulsions mainly occur between 3 months and 5 years of age with a peak in the second year.
- Fever is thought to trigger seizures in genetically predisposed children as 30–50% first-degree relatives have a history of febrile convulsions.
- Respiratory infection is the predisposing cause.
- Seizures are usually brief, bilateral clonic or tonic-clonic fits. Sixty to 70% have single seizure.
- Prolonged febrile convulsions may cause mesial temporal sclerosis and may be responsible for later aferbile fits.
- Febrile convulsions are ***simple*** when generalized, duration less than 15 minutes long and do not recur.
- Febrile convulsions are ***complex*** when focal, prolonged more than 30 minutes or multiple in 24 hours period and family history of convulsive disorder is present.
- Meningitis must be ruled out.

Table 14.11: Febrile convulsions.

Febrile convulsions	
Age	5% children affected between 6 months to 5 years
Common causes	Mostly viral Upper respiratory tract infection Acute otitis media/mastoiditis Pharyngitis/Adenoiditis Urinary tract infection
Benign attack	Lasts less than 10 minutes First convulsion, no recurrence in same illness. No family history of febrile seizures
Atypical febrile convulsion	Convulsion lasts more than 10–15 minutes Repeated history of febrile seizures Family history of epilepsy/febrile seizures Known neurological deficit

Diagnosis

- Blood count
- Lumbar puncture if required
- Blood sugar, calcium, phosphorus, urea and electrolytes
- An EEG is indicated if febrile seizure is complicated. EEG should be done at least a week after the illness to prevent transient findings in EEG due to fever or seizure itself.

Management

- Measures to control fever, and appropriate antibiotics (if a bacterial illness is suspected or found) are the mainstay of treatment.

Control seizure

- Diazepam 0.2 mg/kg slow diluted IV OR
- Give phenobarbitone 5 mg/kg slow diluted IV injection
- Paraldehyde 0.15 ml/kg PR diluted in mineral oil

Lower the temperature

- By tepid water sponging and antipyretics like Paracetamol 60 mg/kg/day

Family should be reassured

Prophylactic anti-convulsants

- These are not indicated in uncomplicated febrile seizures.
- Prophylactic anti-convulsants are indicated:
  - If febrile seizures are complicated or prolonged.
  - If medical reassurance fails to relieve the anxiety of parents.
- Diazepam is used at the onset of fever and continued for the duration of the febrile illness.
- Alternatively, phenobarbitone 3–5 mg/kg/day is given as a single dose. It cuts the recurrence by two third and may be recommended for 2 years in:
  - Patients under 18 months with abnormal development
  - Complex seizures
  - Positive family history of febrile convulsions
- Sodium valproate may also be used as a prophylaxis.
- Phenytoin and carbamazepine are not effective as prophylaxis of febrile seizures.

Risk factors for recurrence of febrile seizures

Major

- Age <1 year
- Duration of fever <24 hour
- Fever 38–39°C (100.4–102.2°F)

Minor

- Family history of febrile seizures
- Family history of epilepsy
- Complex febrile seizure
- Male gender
- Lower serum sodium at time of presentation

Having no risk factors carries a recurrence risk of approximately 12%, one risk factor 25–50%, two risk factors 50–59%, three or more risk factors 73–100%.

Prognosis

- It is good in simple febrile convulsions but infant with complex febrile seizure may develop epilepsy later in life.
- About 6% children develop psychomotor epilepsy following prolonged unilateral fits before the age of 3 years.
- The younger the child, the more likely it is that febrile convulsions will recur.

Factors that influence the recurrence rate are:

- Abnormal development before first febrile seizure
- A history of afebrile seizure in parents and siblings
- The number of subsequent febrile illnesses
- About 50–75% of recurrences take place within 1 year of initial seizure, and about 90% occur within 2 ½ years.
- Recurrence rate can be influenced by the intermittent use of rapid acting anti-epileptic drugs or continuous prophylactic treatment.

EPILEPSY

CASE

A 4-year-old girl presents with history of off and on fits with loss of consciousness. There is history of excessive salivation ad tongue bite during attacks. She is mentally normal.

Definition

- A **seizure (convulsion)** is defined as a paroxysmal involuntary disturbance of brain function that may be manifested as an impairment or loss of consciousness, abnormal motor activity, behavioral abnormalities, sensory disturbances, or autonomic dysfunction.
- **Epilepsy** is defined as recurrent seizures unrelated to fever or to an acute cerebral insult.

Incidence/etiology

- Seizures are common neurologic problems in pediatrics.
- Seizures occur in 3–5% of children. Approximately 0.5–1.0% of children have epilepsy.
- About 60% of all cases of epilepsy start in childhood.
- In about half of all children with recurrent seizures, the workup will not disclose a specific cause.
- There are many causes of epilepsy.
- In general, any event having the potential to produce insult to the brain can result in epilepsy.
- Mostly the cause is a static or non-progressive encephalopathy secondary to hypoxia, hemorrhage, CNS infection, head trauma, or developmental defects of the brain.
- Labor and delivery complications are also less common cause of epilepsy.
- Other important entities to be considered are tuberous sclerosis, neurofibromatosis, brain tumors, some inborn errors of metabolism, and certain degenerative brain diseases.
- The chance of having a second seizure after an initial unprovoked episode is 30%.
- The chance of remission from epilepsy in childhood is 50%.
- The recurrence rate after the withdrawal of drugs is about 30%.

Evaluation

- Epilepsy is a clinical, not a laboratory, diagnosis.

History

- Age of onset of first seizure
- Duration and frequency of seizures

- Factors that may have precipitated the seizures (e.g. fever)
- Seizures are focal or generalized in onset
- Presence of auras
- Postictal confusion, sleep, or (Todd) paralysis (on one side implies a focal onset)
- Any developmental delay
- Previous drug treatment for epilepsy or for other illnesses

Physical examination

- Exclude some organic cause
- Take head circumference
- Observe the facial (dysmorphic) features
- Complete CNS examination for any focal neurological signs
- Development assessment
- Birthmarks such as café-au-lait spots or hypopigmented macules may point to a neurocutaneous syndrome
- Fundoscopy for papilledema, chorioretinitis, retinal hamartomas, and other congenital anomalies

Table 14.12: Classification of epileptic seizures and some epileptic syndromes.

Generalized Seizures	Tonic-clonic Myoclonic Absence • Typical • Atypical Atonic Tonic Clonic
Partial seizures	**Simple partial** (consciousness not impaired) • Motor signs • Special sensory • Autonomic • Psychic **Complex partial** (consciousness impaired) • Impaired conscious at onset
Unclassified seizures	Neonatal seizures
Epileptic syndromes	• Benign focal epilepsy • Juvenile myoclonic epilepsy • West syndrome • Lennox-Gastaut syndrome

GENERALIZED SEIZURES

- These involve both cerebral hemispheres initially and characterized clinically by an abrupt arrest of activity and an immediate loss of consciousness.
- **Tonic phase** consists of sustained, generalized contraction of flexor or extensor muscles. It usually lasts for only a few seconds.
- **Clonic phase** follows the tonic phase and is characterized by the symmetric, rhythmic, clonic activity consisting of alternating contraction and relaxation of major appendicular or axial muscle groups.
- Clonic phase is longer in duration than the tonic phase. It often terminates spontaneously in less than 5 minutes. During clonic phase, respiration may be irregular and there may be sphincter incontinence.
- After clonic phase, usually there is a variable period of confusion and lethargy, which may persist for minutes to hours, and sleep is common.

Grand mal epilepsy (tonic clonic seizures)

- It is the most common convulsive disorder after infancy.

Etiology

- Idiopathic (when no cause can be found).
- Organic (Secondary)
  - Post–traumatic from laceration of brain tissue
  - Post–hemorrhagic from birth injury or hemorrhage
  - Post–infectious following meningitis, encephalitis
  - Post–toxic e.g. Kernicterus, lead, arsenic, etc.
  - Degenerative brain diseases e.g. cerebromacular degeneration, tuberous sclerosis, neurofibromatosis, etc.

Clinical findings

Aural stage

- It occurs in less than a third of patients.
- It is the warning stage and may be divided into motor or sensory aura.
- In motor aura there is twitching or localized spasm and in sensory aura patient sees abnormal lights or complains of headache or ringing in the ears. The intervening period is usually short which may be hours or even a day or two.

Tonic–clonic stage

- Tonic stage precedes clonic stage in children or there may not be any differentiation.
- The onset of paroxysm is abrupt and with the onset of tonic spasm patient loses consciousness and may fall to the ground. The face becomes pale. The eyeballs roll upward, pupils dilate, conjunctivae becomes insensitive, head is retracted back, the abdominal and chest muscles are held rigidly and limb muscles stiffen out. As air is forced out of the lungs through the closed glottis by sudden contraction of the diaphragm, a startling cry may be heard. The tongue may be bitten by contraction of the jaw muscles. Micturation and defecation may occur. As tonic phase continues, facial pallor is followed by clonic phase. Seizures are predominantly tonic during infancy.

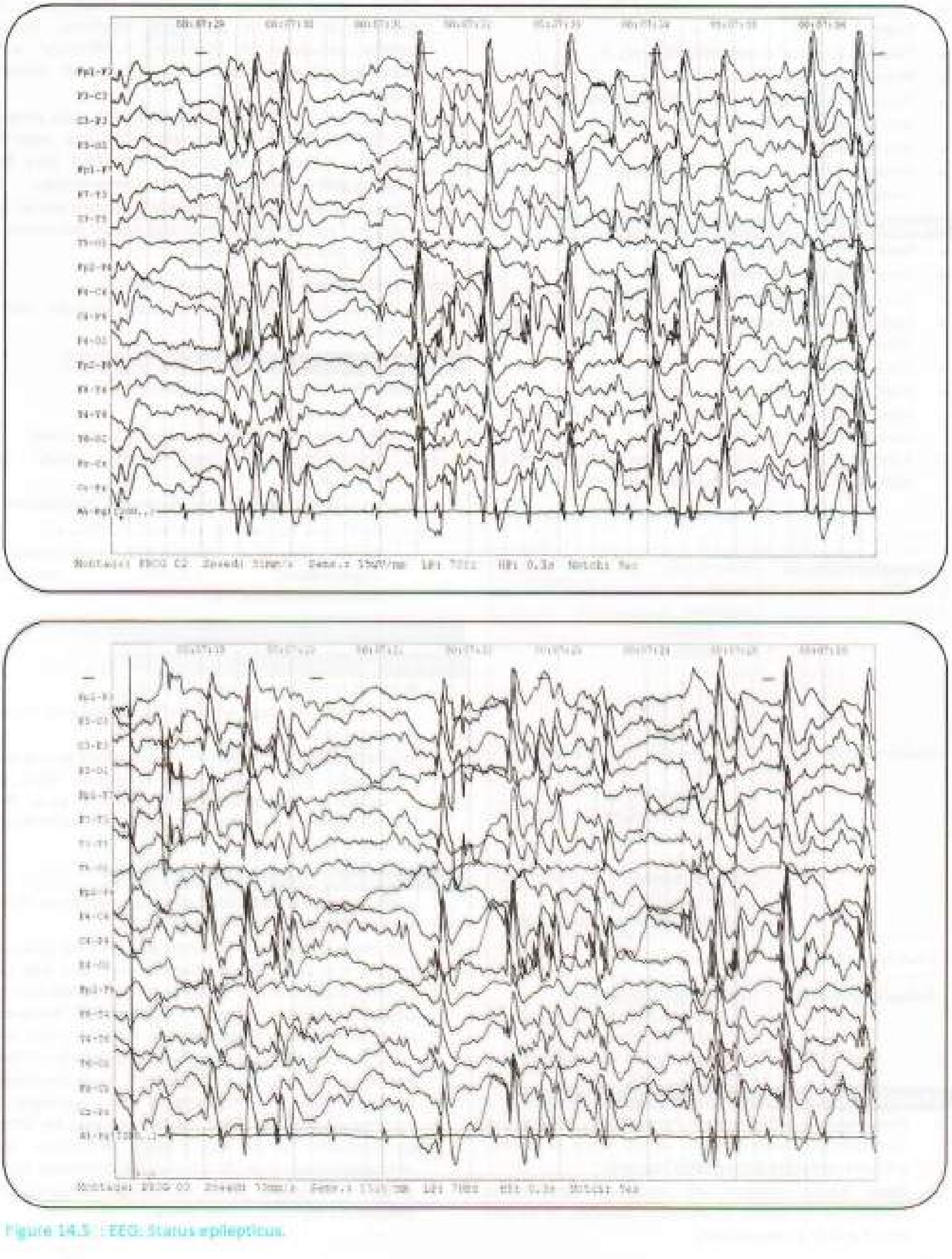


Figure 14.5 : EEG: Status epilepticus.

- The clonic phase is characterized by rhythmic shaking of the trunk and extremities and frothing in the mouth. This stage lasts for about 2–5 minutes.

Postictal stage

- Following convulsions the patient is exhausted and goes to sleep for a few hours and when he awakes there may be severe, generalized headache and state of confusion.
- Transient paralysis may occur (Todd's paralysis).
- Postictal reactions occur due to malfunctioning of the neurons.

EEG

- There are bilateral multiple high voltage spike discharges or spikes and waves during fits.
- Between seizures there are random spike discharges, diffuse high voltage slow waves or pattern consistent with chronological age.

Petit mal epilepsy (absence seizures)

CASE

A 10-year-old boy is not focusing on studies for the last three months. Parents explain that while talking, he *suddenly starts seeing blankly for a while*. In this condition, on calling his name, he takes few seconds to respond. After this episode, he does not recall what he was looking at. Rest of clinical examination is normal.

- It is the next most frequent type of convulsions in children.
- It rarely occurs before 5 years of age and frequently disappears by puberty.
- Girls are more often affected than boys. Intellectual development is normal.
- These seizures consist of transient loss of consciousness or vacant stares during which there may be rolling of the eye, blinking or nodding of the head.
- Multiple episodes may affect school performance or behavior.
- These attacks usually last less than 30 seconds and patient does not fall but may drop articles or stop writing or reading. Patient does not lose body tone, but their head may fall forward slightly.
- Immediately after the seizure, patients resume pre-seizure (previous) activity. There is aura or postictal depression. These features tend to differentiate absence seizures from complex partial seizures.
- Hyperventilation (for 3–4 min) or flickering light may evoke typical episodes.

EEG

- During attacks there is characteristic 3 per second spike-wave pattern.

Myoclonic epilepsy

- It is characterized by frequent recurrence of brief minor seizures, mainly brief muscle contractions or atonia resulting in multiple falls.
- It is associated with mental retardation and is resistant to drugs.
- It can be divided into several types.

Benign myoclonus of infancy

- It consists of clusters of myoclonic movements confined to the neck, trunk, and extremities. EEG is normal.

Typical myoclonic epilepsy of early childhood

- Birth history is normal.
- Mean age of onset is 2 ½ years (6 months–4 years).
- EEG shows fast spike wave complexes of ☐2.5 Hz and a normal background rhythm.
- 1/3rd children have a positive family history of epilepsy.
- Prognosis is favorable.

Complex myoclonic epilepsies

- Prognosis is poor.
- 1/3rd have delayed developmental milestones.
- History of hypoxic-ischemic encephalopathy may be present.
- There are generalized upper motor neuron and extrapyramidal signs with microcephaly.
- Family history of epilepsy is not common.

Juvenile myoclonic epilepsy (Janz syndrome)

- It usually occurs between the ages of 12–16 years.
- Child experience frequent myoclonic jerks on awakening and the myoclonus tends to abate later in the morning.
- After some years, early morning generalized tonic-clonic seizures develop in association with the myoclonus.
- Neurologic examination is normal.
- They respond effectively to valproate, which is given for life.

Progressive myoclonic epilepsies

- This is a rare genetic disorder.
- It has a poor prognosis.

PARTIAL SEIZURES

- In these, only one cerebral hemisphere is activated.
- Partial seizures account for up to 40% of childhood seizures.
- In simple partial seizures, consciousness is not impaired during the attack whereas in complex partial seizures, consciousness is lost.

Simple partial seizures

- Consciousness is maintained during simple partial seizures.
- Patient may verbalize during the seizure.

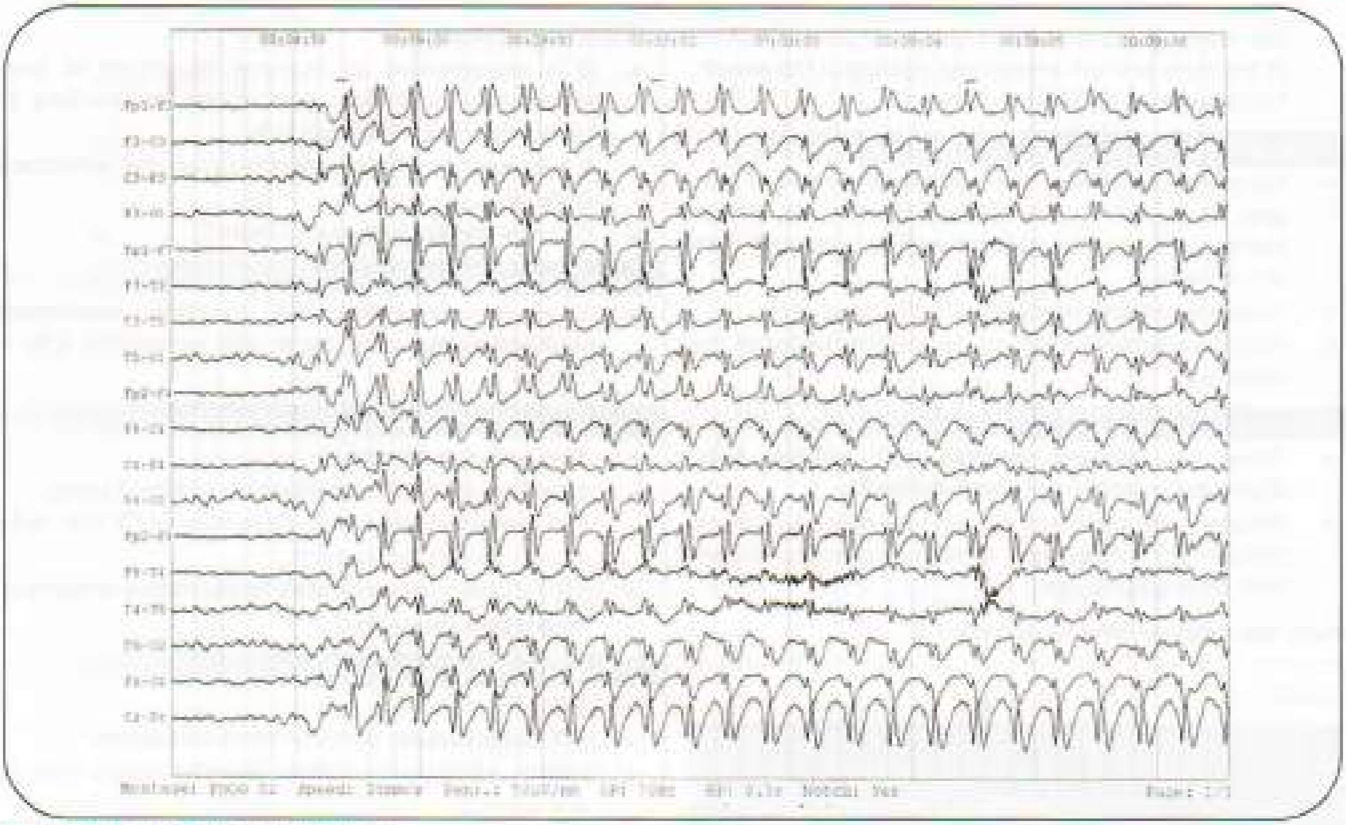


Figure 14.6 : EEG: Absence seizures.

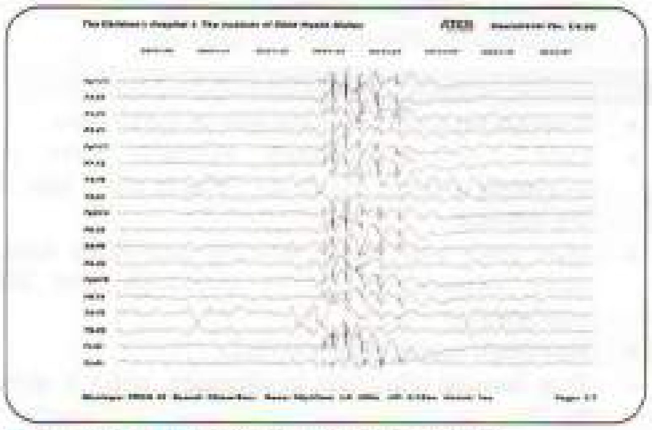


Figure 14.7 : EEG: Juvenile myoclonic epilepsy.

- No postictal phenomenon follows the seizures.
- Motor activity is the most common symptom of simple partial seizures. Asynchronous clonic or tonic movements are seen in the face, neck, and extremities.
- Automatism does not occur in simple partial seizures. An aura may be present.
- Seizure lasts for 10–20 seconds.
- EEG shows spikes or sharp waves unilaterally or bilaterally or a multifocal spike pattern in patients with simple partial seizures.

Complex partial seizures

- A complex partial seizure may begin with a simple partial seizure with or without an aura, followed by impaired consciousness.
- An aura (vague unpleasant feelings) is present in 1/3rd of children with simple partial seizures and complex partial seizures. The presence of an aura always indicates a focal onset of the seizure.
- Automatisms are a common feature of complex partial seizures (50–75% of cases). The automatic behavior in infants is characterized by lip smacking, chewing, swallowing, and excessive salivation. Automatic behavior in older child includes semi-purposeful, uncoordinated, and unplanned gestural automatisms (e.g. picking and pulling at clothing or the bed sheets, rubbing objects, and walking or running in a non-directive, repetitive, and often fearful fashion).
- Complex partial seizures can evolve into a generalized tonic–clonic convulsion.
- The average duration of a complex partial seizure is 1–2 minutes.
- Interictal EEG shows sharp waves or spikes in the anterior temporal lobes. Spikes in the frontal, parietal, and occipital lobes are less common.
- MRI may show lesions in the temporal lobe.

Jacksonian epilepsy

- It may be sensory or motor and signs will vary with the focus of involvement.
- Seizure may start from any part of body and spread to become generalized (Jacksonian march) and consciousness is lost when generalized convulsions occur.

- Benign rolandic epilepsy accounts for 15–20% of childhood epilepsies. It occurs between 3–10 years of age and usually during sleep.
- It starts as facial muscles twitching and extends to arm or rarely to leg. Patient may be unable to speak while perfectly conscious.
- EEG shows spikes localized to the rolandic area on one side.
- There are no mental abnormalities and seizure disappears before 10–14 years of age.

Psychomotor or temporal lobe epilepsy

- Clinical features consist of altered sensory behavior such as bad smell or taste, auditory or visual hallucinations, feelings of familiarity (déjà vu) or strangeness.
- Motor phenomena include licking, chewing, and swallowing, undressing or mumbled speech.
- In a small child, he suddenly stares, is out of contact, looks frightened and clings to the mother.
- The child emerges from the fit with intense tiredness.
- The duration is more than 30 seconds and postictal fatigue differentiates it from petit-mal.
- In psychomotor epilepsy, neurologic signs, intellectual defects and hearing problems are common.
- The seizures are refractory to treatment.
- EEG: It localizes discharges to the temporal lobe.

EPILEPTIC SYNDROMES

Infantile spasm (west syndrome)

CASE

A 5-month-old ***infant*** presents with repeated brief ***spasms of head nodding*** with ***arms extending***. EEG shows ***hypsarrhythmia***.

- These occur from 3–9 months of age and consist of sudden forward flexion of the head, bending of the knees and flexion of the arms (salaam seizures).
- Occasionally spasm is in extension resembling a Moro response.
- The spasms last a few seconds and recur several times.
- Symptomatic infantile spasms occur in patients with brain damage from prenatal insult, birth asphyxia, postnatal insult, brain malformations and tuberous sclerosis. The prognosis is poor and they have 80–90% risk of mental retardation.
- Only 10–20% of infantile spasms are classified as cryptogenic, in which the children have normal development and physical examination and no associated risk factors. Infants with cryptogenic infantile spasms have a good prognosis.
- The EEG shows characteristic hypsarrhythmia, a chaotic pattern of high-amplitude slow waves and spikes.
- Treatment: Nitrazepam, Clonazepam, ACTH, Prednisolone.

Lennox–Gastaut syndrome

- This syndrome is characterized by the triad of:
    - Intractable seizures of various types
    - A slow spike wave EEG during the awake state
    - Mental retardation
- It occurs between 2–7 years of age and consists of very frequent, brief tonic, myoclonic, or atonic fits, which result in multiple falls daily with injuries.
- Occasionally there is clouding of consciousness with head nodding and massive myoclonias.
- Treatment with valproic acid or the benzodiazepines may decrease the frequency or intensity of the seizures.
- Rivotril and steroids are also given for treatment.

MANAGEMENT OF EPILEPSY

Deciding on long-term therapy

- After a first seizure, if the risk of recurrence is low (such as when the patient has normal neuro-developmental status, EEG, and MRI), then treatment is usually not needed.
- If the patient has abnormal EEG, MRI, development, and/or neurologic exam, and/or a positive family history of epilepsy, then the risk is higher and treatment is started.
- The decision is mostly individualized and all aspects of this decision should be discussed with the family.

Principles of anticonvulsant therapy

- Treat with the drug appropriate to the clinical type of epilepsy.
- In general, the drugs of first choice:
    - For focal seizures and epilepsies are oxcarbazepine and carbamazepine
    - For absence seizures ethosuximide
    - For juvenile myoclonic epilepsy valproate and lamotrigine
    - For Lennox-Gastaut syndrome clobazam, valproate, topiramate, lamotrigine, and rufinamide
    - For infantile spasms, adrenocorticotropic hormone (ACTH)
- Do not use the anticonvulsant drug used previously without any success.
- Start with the one drug of choice in appropriate dosage. Increase the dose until seizures are well controlled or signs of toxicity appear.
- If seizures are not controlled with one drug of choice, second drug of choice is added. Do not stop first drug suddenly. Withdraw it gradually.
- Advise the parents and the patient that the therapy will be prolonged but it will not produce any mental slowing. Changes in medications or their dosages

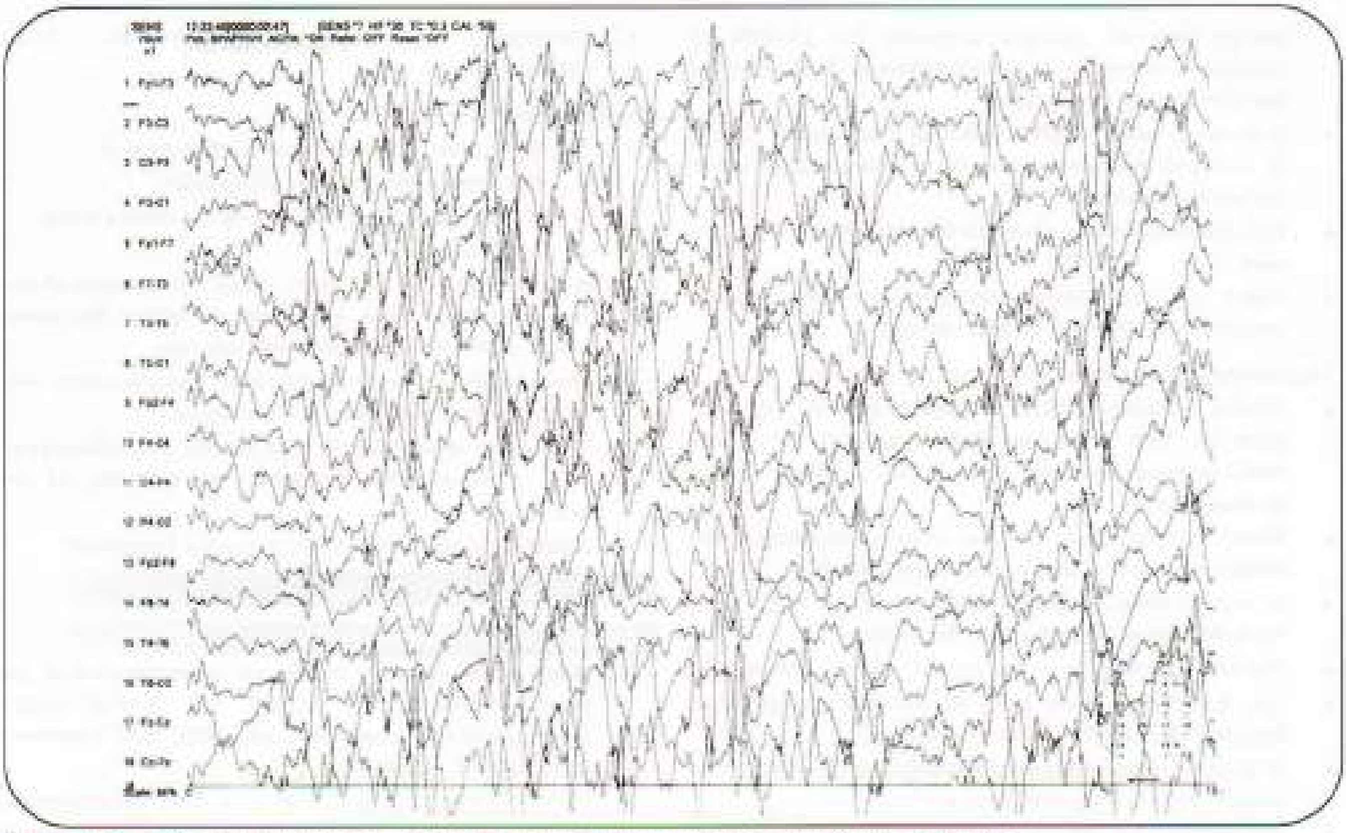


Figure 14.8 : EEG: Hypsarrhythmia, a chaotic pattern of high amplitude slow waves and spikes

should not be made without the advice of the physician. Sudden withdrawal of anticonvulsants may precipitate the seizures or even status epilepticus.

- Follow up of the patient and periodic neurologic re-evaluation is important.
- If signs of toxicity appear, then reduce the drug by 25% or add another drug.
- Get frequent blood levels of anticonvulsant drugs as required.
- After 2–3 years of fits free interval, consider withdrawal of the anticonvulsant drug. Withdrawal should be gradual. In about 75% of cases, seizures may not recur. If seizures recur during or after withdrawal, anticonvulsant therapy should be reinstituted and again maintained for at least 2 or more years. Generally, an EEG is indicated before withdrawal of an anticonvulsant. In case of an abnormal EEG, withdrawal may be deferred for 2–3 years.

Determination of blood levels of anti-convulsants

- Other drugs may affect blood levels of anticonvulsants. In such cases, adjustment of doses may be required.
- Drug blood levels are indicated in a new patient, after a new drug is introduced, when expected control on a usual dosage has not been achieved, when seizures recur in a previously well-controlled patient, or when control is poor in a patient taking anticonvulsants being seen for the first time.

Table 14.13: Drug interactions

Drug	Levels increased by	Levels decreased by
Carbamazepine	Erythromycin Cimitidine	Phenobarbitone Phenytoin
Valproic acid	Lamotrigine Cimitidine	Phenobarbitone Phenytoin Carbamazepine Lamotrigine
Phenytoin	Phenobarbitone	Carbamazepine Phenobarbitone Antacids

- A low level may indicate inadequate dosage, drug interaction, or noncompliance with the prescribed regimen.
- A high level may indicate slowed metabolism or excretion or drug interaction.

Education about the disease

- The patient and parents must be helped to understand the problem of seizures and their management.
- Materials about epilepsy must be provided.
- Advise that the child should be very careful in cycling on the road, unsupervised swimming, or locking the door of the bathroom when inside.

- Encourage normal living but within reasonable bounds. Physical activities appropriate to their age should be allowed.
- Loss of sleep should be avoided and emotional disturbances may need to be treated.
- Proper attention should be given to infections and it is advised not to stop anticonvulsants in fever or in any other illness.

ACTH and corticosteroids

- These are indicated in infantile spasms and in Lennox-Gastaut syndrome.
- ACTH or oral corticosteroids are usually continued in full doses for 2 weeks to 2 months and after normalization of EEG and cessation of clinical seizures, tapered over 1 week.
- Dose of ACTH gel is 2–4 units/kg/day IM in a single morning dose.
- Prednisolone is given 2–4 mg/kg/day orally in two or three divided doses.

Ketogenic or medium-chain triglyceride diet

- A ketogenic diet should be recommended in myoclonic and absence seizures not responding to drug therapy. It is occasionally recommended for infantile spasms that do not respond to ACTH or corticosteroid therapy.
- Ketosis induced by ketogenic diet raises the seizure threshold.

Surgery

- Seizures with primarily focal origin, neurosurgery should be considered for poorly controlled seizures.

Drugs used in epilepsy

Phenobarbitone

- It is one of the most effective drugs. It is cheap and well tolerated.
- It is useful in neonatal seizures and status epilepticus.
- Side effects: it causes drowsiness, ataxia, allergic reaction such as skin rash and fever and sometime hyperactivity and irritability. It may interfere with learning. Avoid phenobarbitone in school going children as it causes school failure and aggressiveness.
- Dose is 3–5 mg/kg/day bid or qid.

Phenytoin

- It is also very effective and does not cause sedation.
- Side effects are hypertrophy of the gums, hirsutism, megaloblastic anemia, agranulocytosis, skin rash, ataxia, diplopia and tremors. Avoid long term use in girls for cosmetic effects.
- Dose is 5–10 mg/kg/day tid.
- Good dental hygiene reduces gum hyperplasia.

Valproic acid

- Its presumed action is to increase the content of GABA (Gammaaminobutyric Acid) in the brain.
- Side effects: nausea, alopecia, hepato-toxicity, weight gain, and thrombocytopenia.
- Avoid valproic acid in children less than 18 months of age and in those with liver dysfunction.
- Advantage: No drowsiness and children look brighter and more alert.
- Dose is 15–40 mg/kg/day tid.
- Monitor CBC, platelets, liver function tests closely in first 6 months, then periodically.
- It can be given rectally.

Carbamazepine

- Dose is 10–20 mg/kg/day in 2–4 divided doses.
- Side effects are dizziness, ataxia, diplopia, thrombocytopenia, leukopenia, and rash. Rarely, there is hepatotoxicity, bone marrow depression, dystonia, inappropriate ADH secretion, and bizarre behavior.
- Monitor CBC, platelet count, liver function tests for first 6 months, then periodically. Blood effects are usually early and transient.

Table14.14: Drugs of choice in different types of epileptic disorders.

Type of disorder	Drugs and daily dosage (mg/kg/day)
Grand mal epilepsy	Valproic acid (20–30) Carbamazepine (10-20) Phenobarbitone (5) Phenytoin (5–8)
Petit mal epilepsy	Ethosuximide (15–30) Valproic acid
Focal epilepsy	Carbamazepine (10–20) Valproic acid Phenytoin
Myoclonic epilepsy	Valproic acid (20–30) Clonazepam (0.1–0.25) Ethosuximide
Infantile spasm	ACTH (20–60 IU/day) Prednisolone (1–2)
Psychmotor	Carbamazepine

Lamotrigine

- It is used as adjunctive therapy when seizures are poorly controlled.
- Broad-spectrum anti-convulsant activity in various seizure types including complex partial, absence, myoclonic, clonic, tonic-clonic, and Lennox-Gastaut.
- Dose is 5–15 mg/kg/day in 2–4 divided doses (1–5 mg if taking valproic acid). Increase dose slowly over 2 months.
- Side effects are dizziness, headaches, diplopia, ataxia, nausea, and rash.

Vigabatrin

1. Indicated in refractory seizures (partial, primary generalized, infantile spasms).
2. Side effects are agitation, fatigue, and aggressiveness, weight gain, and drowsiness.
3. Dose: initially 30 mg/kg/day once daily. Maintenance dose is 30–100 mg/kg/day once daily.

STATUS EPILEPTICUS

CASE

A 5-year-old boy is taking medicines for epilepsy. Now, he presents with ***intractable seizures*** and loss of consciousness for the last 1 hour. He has no fever.

Definition

- It is defined as a single generalized or series of tonic convulsions lasting 30 minutes or longer without intervening return of consciousness OR an epileptic seizure which is so prolonged or so frequently repeated as to create a fixed and lasting epileptic condition.
- There are two types of status epilepticus: convulsive and non-convulsive. The latter consists of prolonged absence or complex partial seizures.

Incidence

- It is estimated that 1.3–16% of all patients with epilepsy will develop status epilepticus at some point in their lives.
- In some patients, it is the presenting initial seizure.

Etiology

- Status epilepticus occurs most frequently in patients younger than 1 year of age.
- The etiology differs according to the age group. Two common causes are withdrawal of anti-epileptic drugs and hyperpyrexia secondary to a non-CNS infection in a patient with chronic static encephalopathy or seizure disorder.

Pathophysiology

- Brain damage occurs if the seizures remain for 60 minutes. Cell death results from excessively increased metabolic demands by continuously discharging neurons.
- Areas of brain, which are most vulnerable to damage, are hippocampus, amygdala, cerebellum, middle cortical area, and thalamus. There is venous congestion, small petechial hemorrhages, and cerebral edema.
- There is lactic acidosis, an alteration in the blood-brain barrier, raised intracranial pressure and fever due to prolonged seizures.
- There are raised concentrations of calcium, arachidonic acid, and prostaglandins, which cause cell death.
- There is dysfunction of the autonomic nervous system causing hypotension and shock.

Table 14.15: Common etiologies of status epilepticus.

Neonates	• Hypoxic ischemic encephalopathy • Infection • Inborn errors of metabolism (e.g. non-ketotic hyperglycemia) • Stroke or intraventricular hemorrhage • Congenital malformations • Pyridoxine deficiency and dependency
Child	• Infection • Anticonvulsant withdrawal • Simple febrile seizures • Metabolic disturbances • Congenital malformation • Presentation of epilepsy • Trauma

Management

- It is a medical emergency and requires prompt treatment.
- The main goals of the treatment of status epilepticus are to:
  - Maintain adequate vital functions with prevention of systemic complications.
  - Terminate the seizure activity safely and quickly while minimizing treatment morbidity.
  - Evaluate and treat any underlying cause e.g. hypoglycemia, and meningitis.

Initial stabilization

- Airway: The highest priority is ensuring airway patency. Maintain oral airway. Intubation may be necessary.
- Breathing: Give oxygen to prevent hypoxia.
- Circulation: Assess pulse, blood pressure. Support with IV fluids. Monitor vital signs. Maintain perfusion.
- Measure serum glucose by finger prick.
- Check body temperature. Lowering body temperature is very important. Higher body temperature increases the neuronal discharges and the tissue damage associated with status epilepticus.
- If vomiting occurs, turn the face to side and lower the head.
- Venous access should be established as quickly as possible.
- Blood is drawn for immediate complete blood count and measurement of electrolytes, glucose, calcium, and magnesium concentrations, toxic screen and levels of anticonvulsant medications if the child is already receiving therapy for seizures.
- The initial stabilization phase of patient with status epilepticus is usually accomplished within the first 10 minutes after presentation to the emergency department. Specific anticonvulsant therapy is then started.

Drug therapy

- If finger prick sample indicates blood glucose <50 mg/dl, treatment is initiated for hypoglycemia (2–4 ml/kg of 25% dextrose; 0.5–1.0 g/kg).
- A benzodiazepine is the first drug used because of its rapid onset of action. Diazepam is given 0.2 mg/kg IV up to 6 mg over 1–2 min. May be repeated after 5–6 minutes for total of three doses. Duration of action is only 20 minutes. In the absence of I/V access, diazepam can be given effectively by the rectal route. Rectal diazepam is given without dilution by inserting the smallest possible syringe or a small catheter on the end of the syringe. If the dose is less than 5 mg, a tuberculin syringe is ideal. The medication should be placed a distance of 4 cm into the rectum adjacent to the rectal mucosa. The buttocks should be elevated and squeezed together for 5 minutes to avoid evacuation of the rectal contents following administration of the drug. Diazepam may be repeated twice, 5–10 minutes apart.
- Because the half-life of diazepam is very short, it must be followed immediately by phenytoin. Dose is 20 mg/kg IV in normal saline. It precipitates in glucose solutions. It must not be given I/M. Give 1/3rd of dose over 1–2 minutes and remaining as 1 mg/kg/minute infusion or slower if bradycardia or hypotension occurs. Phenytoin is preferable to phenobarbitone because of the increased incidence of respiratory depression associated with combined use of phenobarbitone and diazepam. Phenytoin is less sedating than phenobarbitone and may make it easier to follow neurological vital signs in these patients.
- If seizure activity continues for another 5–6 minutes, give 1 ml/kg sodium bicarbonate to treat metabolic acidosis that will have developed after continuous seizure activity of this duration.
- If status does not stop within 10 minutes of the total dose of phenytoin being given, phenobarbitone is the next drug. Dose is 20 mg/kg IV up to 800 mg over 10 minutes. It is slow acting (effective concentrations in brain are achieved in 15–30 minutes). You must be ready to intubate a patient who has received a benzodiazepam and phenobarbitone.
- If status is not responsive to a benzodiazepine followed first by phenytoin and then by phenobarbitone, the patient will require further therapy as given below.
- Paraldehyde 0.3 ml/kg PR mixed with equal amount of mineral oil in a glass syringe.
- Valproic acid 40–60 mg/kg/dose PR diluted 1:1 with tap water.
- Lidocaine 1–2 mg/kg IV up to 50–100 mg bolus over 2–4 minutes followed, if effective, by 3–5 mg/kg/hour as solution of 100–1000 mg in 250 ml 5% dextrose.
- Halothane anesthesia is given by anesthesiologist, titrated to suppression of discharges on EEG.
- Note: When a drug is selected to be used, sufficient time must be allowed for the drug to act before more of the same medication or another medication is used. If a single agent does not control the seizures, a second drug may be needed. I/V and rectal administration are the routes of choice.

Postictal management

- Give maintenance drug therapy by phenytoin (10 mg/kg/day) or phenobarbitone 5 mg/kg/day).
- LP should be deferred until the patient's vital signs are stable and the convulsions have stopped. If sepsis is felt to be likely, I/V antibiotics may be given immediately without waiting to do the lumbar puncture.
- A history of trauma, evidence of raised intracranial pressure, focal neurologic signs, unexplained loss of consciousness or suspicion of cerebral herniation are indications for CT scan.

Prognosis

- Mortality and morbidity (cognitive or motor deficits) depend primarily on the cause and the underlying condition of the child rather than the actual seizure.
- Mortality from status epilepticus is rare in children who have idiopathic or febrile status epilepticus. However, mortality within 3 months among those who have acute symptomatic status or status related to a progressive encephalopathy is 10% to 15%. Death can be caused by the underlying disease or result from respiratory, cardiovascular, or metabolic complications.
- Subsequent seizures (in 30% of cases) are more likely than residual neurologic dysfunction in a child who presents with status epilepticus. The risk for recurrence of status is considerably lower than the risk for recurrence of seizures.
- The febrile child who presents with status epilepticus and has not had a previous seizure should be started on anticonvulsant therapy. If evidence of primary generalized epilepsy is clear and the child is more than 2 years of age, valproic acid should be used. If there were any focal features during status on examination or in the EEG, carbamazepine is the drug of choice. Children with febrile status should get such treatment for 2 weeks to 3 months.
- The primary complications associated with status epilepticus are the side effects of therapy and systemic effects caused by the prolonged seizure. Complications of status epilepticus include hypoxia, lactic acidosis, hyperkalemia, hypoglycemia, shock, hyperpyrexia, renal failure, and pulmonary failure.
- Infants and younger children tend to exhibit a higher risk for neurologic sequelae, which may include mental retardation, behavioral disorders, focal motor deficits, and chronic epilepsy, than older children.

- Seizures must persist longer than 1 hour before permanent neurologic changes develop.

HEADACHES

- Headaches are one of the most common neurologic symptoms of childhood.
- Headache is caused by inflammation or compression of blood vessels, muscles, or nerve roots.
- It is important to differentiate headaches caused by systemic illness or increased intracranial pressure.

MIGRAINE

CASE

> A 9-year-old girl presents with the complaint of severe, ***recurrent headaches*** for the last several months. Sometimes headache is throbbing over the left eye and is associated with a visual ***aura***. Her mother also has history of migraines. The ***physical examination*** including, a neurologic examination, is ***normal***.

- Migraine is characterized by recurrent attacks of headache that are pulsatile in character and sometimes unilateral.
- Migraine is often accompanied by neurologic disturbances, nausea, vomiting, and photophobia.
- These attacks may be precipitated by stress or ingestion of certain food (e.g. chocolate, peanuts).

Clinical findings

- Patient has an aura preceding the attack (e.g. flashing lights).
- Headache is usually unilateral and pulsatile.
- It is associated with gastrointestinal upset and photophobia.
- Patient feels relief with sleep.
- Physical examination is typically negative.
- There may be positive family history in 75% of cases.

Management

- Acetaminophen 15 mg/kg/dose
- Ibuprofen 7.5–10 mg/kg/dose
- Valproic acid 20 mg/kg/24 hours (begin 5 mg/kg/24 hours then increase 5 mg/kg every 2 week).
- Vasoconstrictors (ergotamine). Dihydroergotamine IV 0.5 mg/dose every 8 hours (<40 kg) 1.0 mg/dose every 8 hours (>40 kg)
- Calcium channel blockers
- Propranolol 10–20 mg tid, begin with 10 mg/24 hours increase 10 mg/week (contraindicated in asthma and depression).

TENSION HEADACHE

CASE

> **Tension headache:** An 8-year-old girl presents with recurrent ***symmetrical headache***. Headache is gradual in onset. She describes that ***headache is like a band around head***. She is having school problems in studies.

- These are caused by prolonged contraction of scalp and cervical muscles.
- There is generalized or 'bandlike' pain described as constant, squeezing, or aching.
- There is no nausea or photophobia.
- Headaches are precipitated by stress, fatigue, or exertion.
- Neurologic examination is normal.

Management

- Analgesic medications. Acetaminophen 15mg/kg/dose. Ibuprofen 7.5–10 mg/kg/dose.
- Rest
- Removal of stressful circumstances if possible

HEADACHES WITH INCREASED INTRACRANIAL PRESSU

CASE

> **Headache due to brain tumor:** A 10-year-old girl presents with ***daily headache*** for last 2 months. Headache is ***progressively becoming more severe***. Now, her ***gait is becoming more unsteady***. Her headache becomes ***worse during coughing or sneezing***. CT scan of brain shows a posterior fossa tumor.

- Headaches may be a symptom of increased intracranial pressure.
- These are caused by traction on the intracranial arteries.
- Main causes of increased intracranial pressure are hydrocephalus, CNS tumors, and CNS infections.
- Papilledema is a common sign of increased intracranial pressure.
- There may be vomiting.
- There may be 6th nerve palsy, limitation of upward gaze, or increased head size.
- Diagnosis is by CT scan, MRI scan, or lumbar puncture.

Management

- Management of the underlying disorder

COMA

CASE

> A 10-year-old child presents in a state of coma. There is history of head injury during road side accident.

- Coma is a state of altered consciousness in which the patient is unresponsive to any environmental stimuli (i.e. patient cannot be aroused).
- Coma is not a specific disorder, but a sign of Central Nervous System (CNS) dysfunction.
- It may be caused by either a primary or a systemic condition affecting the CNS.
- A patient in coma is unresponsive to any environmental stimuli.

Common causes of coma

Infectious disorders

- Meningitis
- Encephalitis (e.g. herpes simplex)
- Cerebral malaria
- Severe systemic dysfunctions

Metabolic disorders

- Hypoglycemia
- Diabetic ketoacidosis
- Hepatic encephalopathy
- Hypoxia
- Uremia
- Electrolyte disturbances

Trauma

- Subdural and epidural hematoma
- Parenchymal bleeding

Poisoning

- Barbiturates
- Opiates
- Aspirin
- Carbon monoxide poisoning
- Lead

Circulatory disorders

- Shock
- Hypertensive encephalopathy

Respiratory failure

- Airway obstruction
- Pulmonary disease

Miscellaneous

- Tumors
- Seizures (postictal state)
- Heat stroke
- Space occupying lesions

Table 14.16: Glasgow Coma Scale (GCS=E+M+V).

Pediatric Glasgow Coma Scale (PGCS)				
	>1 Year	**<1 Year**		**Score**
Eye Opening	Spontaneously	Spontaneously		4
	To verbal command	To shout		3
	To pain	To pain		2
	No response	No response		1
Motor Response	Obeys	Spontaneous		6
	Localizes pain	Localizes pain		5
	Flexion—withdrawal	Flexion-withdrawal		4
	Flexion—abnormal (decorticate rigidity)	Flexion-abnormal (decorticate rigidity		3
	Extension (decerebrate rigidity)	Extension (decerebrate rigidity)		2
	No response	No response		1
	>5 Years	**2–5 Years**	**0–23 months**	
Verbal Response	Oriented	Appropriate words/phrases	Smiles/coos appropriately	5
	Disoriented/confused	Inappropriate words	Cries and is consolable	4
	Inappropriate words	Persistent cries and screams	Persistent inappropriate crying and/or screaming	3
	Incomprehensible sounds	Grunts	Grunts, agitated, and restless	2
	No response	No response	No response	1
			Total Pediatric Glasgow Coma Score (3–15)	

Minimum score = 3

Maximum score = 15

Mild head injury = GCS 13–15

Moderate head injury = GCS 9–12

Severe head injury = GCS 8 or less

Clinical evaluation of coma

- In a comatose patient, before taking history, physical examination or diagnostic procedures make sure that:
  - Patient has a clear airway
  - Patient is not in shock
  - There is no bleeding from a wound (if trauma has occurred)

History

- Onset of comatose condition (gradual or sudden)
- Fever
- Headache
- Vomiting
- Jaundice
- History of any drug intake
- Head trauma
- Convulsions
- Exposure to excessive heat
- Any previous illness (diabetes, hypertension, hepatic or renal failure, or bleeding disorder)

Examination

Vital signs

- Vital signs provide information regarding adequacy of circulation and may give clues to the diagnosis.
- Temperature:
  - Fever suggests severe systemic infection, hyperthermia, meningitis, heat stroke, etc.
  - Hypothermia suggests shock or intoxication.
- Respiration:
  - Slow breathing is present in morphine poisoning, metabolic alkalosis or central respiratory failure.
  - Deep, sighing breathing (Kussmaul's respiration) is present in diabetic ketoacidosis, uremic acidosis, salicylate poisoning and pneumonia.
  - Periodic (Cheyne-Stokes) respiration is characterized by periodically alternating episodes of hyperventilation and apnea. It is due to bilateral cortical damage.
  - Atactic or irregular respiratory pattern is seen in ponto-medullary damage or in increased ICP.
  - Metabolic disturbances such as respiratory alkalosis or metabolic acidosis, or a midbrain lesion may cause central neurogenic hyperventilation characterized by rapid regular breathing.
- Pulse rate:
  - Bradycardia in raised intracranial pressure.
  - Tachycardia in shock or arrhythmias.
- Blood pressure:
  - Increased in hypertensive encephalopathy.
  - Decreased in shock, septicemia, and intoxication.

Skin

- Pallor (in hemorrhage)
- Cyanosis (inadequate oxygenation)
- Hemorrhagic rash (in meningococcal infection, bacterial endocarditis)
- Skin turgor (lost in dehydration)
- Sweating (hypoglycemia, shock)
- Dry and hot skin (in heat stroke)

Odor of breath

- Fruity smell (in diabetic ketoacidosis)
- Uriniferous odor (in uremia)
- Mousy smell (in hepatic coma)

CNS examination

- Signs of meningeal irritation:
  - Positive in meningitis or subarachnoid hemorrhage or bulging fontanel
- Pupillary reaction:
  - Metabolic coma or early stage rostral-caudal herniation with interruption of descending sympathetic pathway is associated with small but reactive pupils.
  - Midbrain involvement is associated with non-reactive, mid-position, or mildly dilated (5–7 mm) pupils.
  - Intoxication or poisoning by organo-phosphates, phenothiazines, opiates or pontine lesions is associated with miosis (pupils less than 2 mm in diameter).
  - Pupils are dilated in postictal state, 3rd nerve damage (tentorial herniation), atropine like drugs and sedatives.
- Eye (extra-ocular) movements:
  - In metabolic upset, eyes rove from side to side in random fashion.
  - Absent eye movements are present in dysfunction of brain stem or oculomotor nerves.
  - There is internal squint in 6th nerve palsy due to increased ICP.
  - Eyes are fixed down and laterally with pupillary dilatation in 3rd nerve palsy.
  - Doll's eye reflex: Manually rotate the patient's head from side and watch closely the position of the eyes. In a patient with intact brain stem (midbrain, pons), the eyes remained fixed on a distant spot, as if maintaining eye contact with that spot. In brainstem injury, eyes move in the same direction as patient's head.
- Fundoscopic examination:
  - Papilledema (in raised ICP).
  - Retinal hemorrhages (in subarachnoid hemorrhage or hypertension).
- Motor response:
  - Hemiplegia (in involvement of pyramidal tract).
  - Decerebrate posture (extension and internal rotation of both the upper and lower extremities; it is present in brain stem dysfunction).

   - Decorticate posture (flexion of the upper extremities at the elbow and extension with internal rotation of the lower extremities; it is present in cerebral cortex dysfunction).
   - Ponto-medullary lesions usually are associated with no response to painful stimuli.

Laboratory evaluation of coma

- **Blood counts:** There is leukocytosis in bacterial infections.
- **Blood culture** in case an infection is suspected.
- **CSF examination**: Infections of the CNS and meninges must be suspected in every comatose child, and a lumber puncture for CSF analysis should be performed in all cases except in a case of Space Occupying Lesion (SOL) or raised ICP.
- **CT scan of the head** is indicated in certain cases of head injury, including those associated with coma, and when a space-occupying lesion is suspected.
- **Metabolic screen:** Blood sugar, blood urea, serum electrolytes.
- **Liver function tests** especially in a case of hepatic encephalopathy or Reye's syndrome.
- **Slide for MP** (Malarial Parasite) if cerebral malaria is suspected.
- **EEG** especially if there is seizure activity.

Management

- The main objective of therapy is to find the cause and remove it. If there is no specific therapy, supportive measures must be taken to save the life of the patient.
- Maintain clear airway.
- Give oxygen.
- Patient should be placed on a side in semiprone position to prevent the danger of aspiration.
- Draw blood for metabolic, septic, and toxic screening.
- Suspect hypoglycemia in every case and give 1–2 ml of 25% dextrose water.
- Frequent suctioning is essential.
- Never leave the patient unattended.
- If the patient is in shock, start rapid infusion of volume expansion fluids (blood plasma, normal saline).
- Control of temperature. Prevent extreme hypothermia or hyperthermia.
- Control convulsions by anticonvulsant medications.
- Prevent the patient from falling out of bed.
- Cerebral edema should be corrected by giving IV mannitol and dexamethasone.
- Give adequate nutrition through NG tube when patient is stable.
- Change posture every half an hour to prevent bedsores.
- Care for oral hygiene.
- Care of bladder. Bladder should not be allowed to be distended and pass urinary catheter.
- Care of bowel. Prevent impaction of stools.
- Monitor the Ventilator.
- Physiotherapy to prevent contractures.

Prognosis

- It depends on the cause of the coma.
- Patients with Glasgow Coma Scale (GCS) scores of 3–5 have a satisfactory outcome but have increased chances of memory, speech, language or motor deficits.
- Patients with GCS more than 6 have good outcome.
- Coma caused by hypoxic-ischemic insults has a very poor prognosis.

HYDROCEPHALUS

CASE

A 6-month-old infant is noted to have ***a head circumference greater than the 95th percentile***. He has delayed milestones, head lag and brisk reflexes.

Definition

Hydrocephalus

- It is a congenital or acquired disorder in which there is an excessive accumulation of cerebrospinal fluid (CSF) within the cerebral ventricles.

Non-communicating (obstructive) hydrocephalus

- It refers to conditions in which the ventricular fluid does not communicate with the fluid in the basal cisterns or spinal subarachnoid spaces.
- There is a block of the CSF flow within the ventricular system.
- Main causes are:
   - Aqueductal stenosis
   - Infections
   - Arnold-Chiari malformation
   - Dandy-Walker malformation
   - Klippel-Feil syndrome
   - Mass lesions
   - Abscess
   - Hematoma
   - Tumors and neurocutaneous disorders
   - Vein of Galen malformation

In communicating (non-obstructive) hydrocephalus

- The block is outside the ventricular system or its exit foramina.
- There is failure of absorption from subarachnoid villi.
- Main causes are:
   - Subarachnoid hemorrhage
   - Pneumococcal and tuberculous meningitis
   - Intrauterine infections
   - Leukemic infiltrates (meningeal malignancy)
   - Achondroplasia
   - Basilar impression

  - Benign enlargement of subarachnoid space
  - Choroid plexus papilloma

Physiology: (Formation of CSF)

- CSF is formed in the ventricular system (mainly by the choroids plexus) through the process of active secretion and diffusion.
- Most CSF is produced in the lateral ventricles but about 25% is produced from extra-chroidal sources, including capillary endothelium within the brain parenchyma.
- CSF leaves the ventricular system by way of foramina in the fourth ventricles and circulates into the lumbar and subarachnoid spaces.
- Most CSF is absorbed in the arachnoid villi and then into venous channels of the sagittal sinus.
- In older children and adults, the total CSF volume is 150 ml (total volume of CSF in an infant is approximately 50 ml). Only 25% is within the ventricular system.
- Rate of formation of CSF is 20 ml/hour, and CSF turns over 3–4 times per day.
- Most of the CSF is extra-ventricular.

Pathogenesis

- There are three causes of hydrocephalus:
  - Increased CSF production
  - A block in CSF flow
  - Impaired absorption of CSF

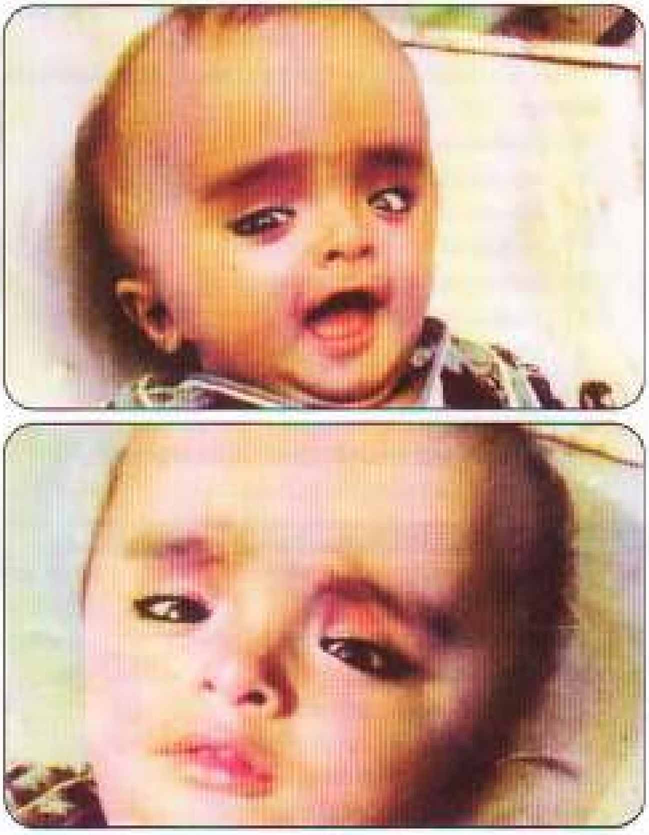


Figure 14.3 : A child with hydrocephalus. Note the sunset sign.

- Most common mechanism for producing hydrocephalus is impaired absorption of CSF due to obstruction of flow or dysfunction of absorptive mechanisms.
- If flow is blocked in the ventricular system, there is dilatation of the ventricles proximal to the block. There is no dilatation distal to the block (disproportionate dilatation). If there is aqueductal stenosis, the lateral and third ventricles are dilated but fourth ventricle is normal.
- If block is extra-ventricular, all ventricles are proportionately dilated.
- Rarely, there is hydrocephalus due to excessive secretion of CSF (e.g. in choroids plexus papilloma).
- Absorption of CSF can be interfered by mechanical obstruction by a tumor, fibrosis of the subarachnoid spaces secondary to bleeding from the tumor, or thrombosis of the superior sagittal sinus.

Etiology

Congenital hydrocephalus: (congenital malformation of CNS)

- Congenital aqueductal stenosis.
- Dandy-Walker malformation: There is massive dilatation of fourth ventricle which obstructs CSF flow and there is hypoplasia of cerebellar vermis.
- Arnold-Chiari malformation type II: The cerebellar tonsils are displaced downward and obstruct CSF flow in meningomyelocele.
- Arachnoid cysts or congenital tumors.
- Intrauterine infections (rubella, CMV, toxoplasmosis, syphilis), cause inflammation of the ependymal lining of the ventricular system or the meninges in the subarachnoid space, so occluding the CSF pathways.

Acquired hydrocephalus

- Secondary to infections of the nervous system (e.g. bacterial meningitis)
- Brain tumors
- Arachnoiditis secondary to bleeding into the subarachnoid space from a ruptured arteriovenous malformation, aneurysm, or trauma
- Intraventricular hemorrhage in preterm infants

Clinical findings

- There are signs and symptoms of the primary process (e.g. tumor, infection, bleeding).
- There are also signs and symptoms of raised intracranial pressure secondary to hydrocephalus.
- Severity of signs and symptoms depend on the rate of the development of hydrocephalus.
- Non-specific symptoms are headache, vomiting, personality and behavior changes (irritability, lethargy, drowsiness).
- Non-specific signs are third and sixth cranial nerve deficits, paresis of extra-ocular muscles leading to diplopia. There may be papilledema.

- There are changes in vital signs (indicating distension of the brain stem).
- Anterior fontanel may become full or distended in young children with large head size (macrocephaly) and a dilatation of scalp veins.
- Sunset sign is produced by paralysis of upward gaze and results in the sclera being visible above the iris.
- In an infant, an accelerated rate of enlargement of the head is the most prominent sign.
- Spasticity develops first in the lower extremities and then in the upper limbs (due to stretching of motor nerve fibers around the bodies of the lateral ventricles).
- There are brisk tendon reflexes, clonus, and Babinski sign.
- There may be cracked-pot or Macewen sign (percussion of the skull may produce a cracked pot like sound indicating separation of the sutures).

Diagnosis

- Serial measurements of head size are important.

CT scan or MRI

- These show the pattern of ventricular dilatation, the presence of interstitial edema (i.e. CSF in the white matter surrounding the ventricles).
- An underlying cause for obstruction of CSF flow is usually readily apparent.

Examination of CSF

- CSF is examined if there is suspicion of a relatively recent infection or if there is a clinical suspicion of subarachnoid bleeding not evident on CT scan.

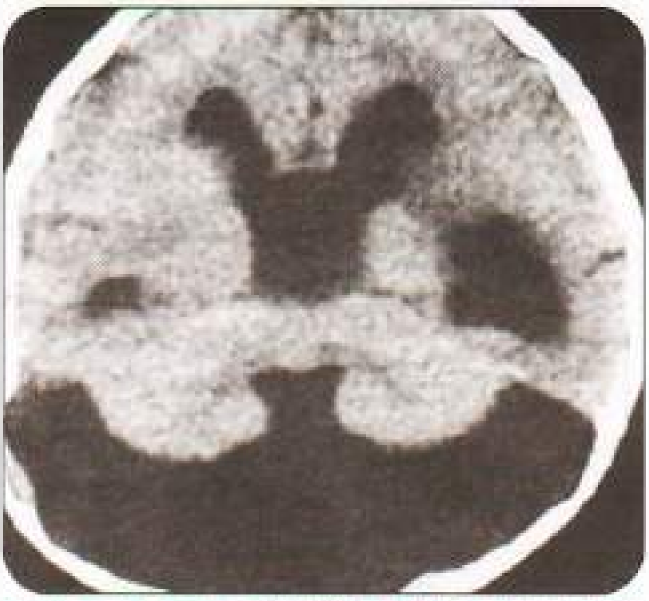


Figure 14.10: CT scan showing findings in Dandy-Walker malformation.

Plain X-ray skull

- It shows separation of the sutures, erosion of the posterior clinoids, and an increase in convolutional markings (beaten-silver appearance). These changes are present if increased intracranial pressure is long-standing.

Differential diagnosis

This includes differential diagnosis of enlarged head secondary to a thickened cranium. Important causes are:

- Chronic hemolytic anemia (thalassemia)
- Rickets
- Osteogenesis imperfecta
- Epiphyseal dysplasia

Management

- Specific therapy for any underlying condition associated with the hydrocephalus (such as meningitis, brain abscess, brain tumor).
- A Ventriculoperitoneal (VP) shunt between the ventricles and the peritoneal cavity is the most effective surgical method of treating progressive hydrocephalus. Complications of shunt are mechanical obstruction, infection of shunt causing meningitis or ventriculitis. Commonly infection is by Staphylococcus epidermidis.
- Medical therapy to decrease CSF production in slowly progressive hydrocephalus includes acetazolamide, furosemide, and glycerol.

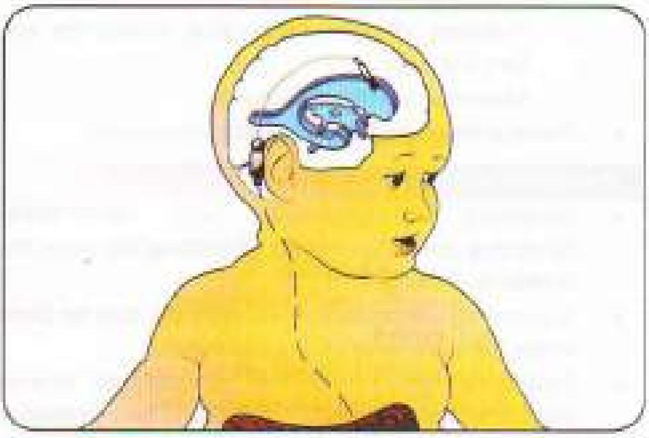


Figure 14.11: Ventriculoperitoneal shunt.

Prognosis

- Prognosis (intellectual and motor function) depends on the nature and severity of the underlying cause of hydrocephalus (intrauterine infections, meningitis, brain tumors, etc.).
- The main disabilities produced by hydrocephalus are motor problems (spasticity or coordination deficits), visual impairments (optic nerve atrophy due to prolonged raised intracranial pressure), and intellectual impairment.
- As gray matter of the brain is less affected by the hydrocephalus than the white matter, intellectual ability is usually less severely affected than motor function.

DANDY–WALKER SYNDROME (MALFORMATION)

- Dandy–Walker syndrome is a congenital brain malformation involving the cerebellum and the fluid filled spaces around it.
- The key features of this syndrome are:
  - An enlargement of the fourth ventricle
  - Complete absence of the cerebellar vermis, the posterior midline area of cerebellar cortex responsible for coordination of the axial musculature
  - Cyst formation near the internal base of the skull
  - An increase in the size of the fluid spaces surrounding the brain as well as an increase in pressure may also be present
- Symptoms, which often occur in early infancy, include:
  - Slower motor development
  - Progressive enlargement of the skull
- In older children, symptoms include:
  - Symptoms of increased intracranial pressure such as irritability, vomiting, and convulsions
  - Signs of cerebellar dysfunction such as unsteadiness and lack of muscle coordination or jerky movements of the eyes
  - Increased head circumference
  - Bulging at the back of the skull
  - Problems with the nerves that control the eyes, face and neck
  - Abnormal breathing patterns
- Prenatal diagnosis is possible with ultrasound.

Management

- Treatment for individuals with Dandy–Walker Syndrome generally consists of treating the associated problems, if needed.
- A shunt to reduce intracranial pressure may be placed inside the skull to control hydrocephalus.
- Treatment also consists of occupational therapy, physiotherapy, speech therapy or specialized education.

INTRACRANIAL SPACE OCCUPYING LESION (SOL)

INTRACRANIAL TUMORS

CASE

A 4-year-old boy presents with severe headache and frequent vomiting since 2 months. He cannot walk normally and has lost the balance of body. There is no history of fever or any head injury. On examination, he is conscious but confused.

Incidence

- Neoplasms of CNS are second to leukemia in frequency and accounts for about 20% of all malignant neoplasms of childhood.
- Peak incidence of brain tumors occurs between the ages of 5 and 10 years.

Classification

- Primary brain tumors can be classified generally by their cell of origin.
- In children over the age of 2 years, 65% of brain tumors are infratentorial and 35% supratentorial.
- In the early stages of acute leukemia, secondary involvement of the nervous system is common.

Table 14.17: Classification of primary brain tumors of childhood.

Tumor type	*Incidence*	*Examples*
Giant cell tumors	50–60%	• Astrocytoma. • Optic nerve glioma. • Brain stem glioma. • Ependymoma.
Neuroectodermal tumors	25–35%	• Medullo-blastoma. • Pinealo-blastoma.
Craniopharyngioma	5–10%	
Germ cell tumors	<10%	• Teratoma. • Dermoid. • Germinoma.
Meningeal tumors	<5%	• Meningioma. • Meningeal sarcoma.
Lymphoma (non-Hodgkin's)	<1%	

- Brain may be involved directly by tumors in the head and neck region that involve extra-neural tissue. Highly aggressive and malignant intracranial tumors (e.g. medulloblastoma) spread throughout the subarachnoid spaces in CNS.

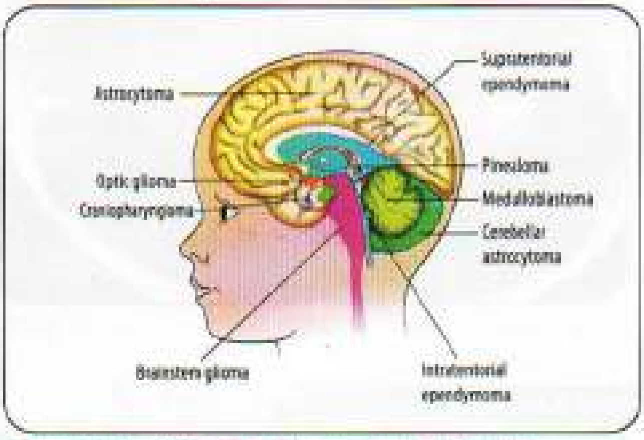


Figure 14.12 : Different brain tumors in childhood.

Clinical findings

- There are non-specific signs due to increased intracranial pressure. These include:

Acute

- Excessive rate of head growth (macrocephaly)
- Altered behavior
- Decreased level of consciousness
- Vomiting
- Blurred or double vision
- Papilledema
- Squint (abducent nerve paresis)

Chronic

- Macrocephaly
- Growth impairment
- Developmental delay
- Optic atrophy
- Visual field loss
    - Infratentorial tumors usually present with gait disturbances, incoordination, nystagmus, and multiple (often asymmetric) cranial nerve palsies.
    - Specific neurological manifestations of supratentorial tumors are according to the location of the tumor. Commonly there are focal motor and sensory abnormalities, focal seizures, and abnormalities of eye movements and vision.
    - In case of hypothalamic or thalamic tumors, there are endocrine and autonomic disturbances.

Diagnosis

CT or MRI scan of the head

- Define the precise anatomic site and extent of tumor.

X-ray skull

- Show scalloping of the inner table of the skull, truncation of the sella turcica, or widening of the suture lines.

EEG (electroencephalogram)

- Not diagnostic in initial evaluation of brain tumor. It may show localized epileptiform discharge in patients with focal or generalized seizures due to tumor.

CSF abnormalities

- Usually, it is not necessary but may be helpful when tumors are disseminated throughout the subarachnoid space.
- It is contraindicated in a suspected case of brain tumor (in such a case CT scan is indicated before CSF examination).

Management

- Treatment is by a combination of surgery, radiation, and chemotherapy.
- Surgery is used to reduce the mass of the tumors.

BRAIN ABSCESS

CASE

A 9-year-old girl presents with history of ***persistent fever*** and ***headaches***. There is an intermittent temperature elevation to 101°F (38.3°C). There is also history of ***vomiting*** and ***frequent otitis media and sinusitis***. On examination, she is lethargic with a temperature of 100°F (37.7°C), heart rate 109/minute and blood pressure 100/60 mmHg. There is also ***nuchal rigidity*** and frontal sinus tenderness. CT scan of brain shows ***a ring enhancing lesion***.

- Brain abscess may appear as systemic illness similar to bacterial meningitis or show signs of focal neurologic defects, papilledema, or other evidence of raised intracranial pressure.
- Most commonly, it occurs between 4 and 8 years of age.
- In about 10–15% of cases, cause of brain abscess is unknown.
- Most brain abscesses are single. In about 30% of cases, brain abscesses are multiple. Multiple brain abscesses may involve more than one lobe.

Conditions predisposing to development of brain abs

- Embolization due to congenital heart disease with right to left shunts (e.g. tetralogy of fallot)
- Endocarditis
- Meningitis
- Chronic otitis media or mastoiditis. Abscesses located in the temporal lobe or cerebellum are frequently associated with chronic otitis media and mastoiditis
- Sinusitis often causes abscess in frontal lobe
- Soft tissue infection of the face or scalp.
- Orbital cellulitis often cause abscess in frontal lobe
- Dental infections
- Chronic pulmonary infections
- Penetrating head injuries. These abscesses are single and are caused by *Staph. aureus*
- Immunodeficiency states
- Infection of ventriculoperitoneal shunts

Etiologic organisms

- Staph. aureus
- Streptococci (viridans, pneumococci, microaerophilic)
- Anaerobic organisms (gram-positive cocci, bacteroides spp, fusobacterium spp, actinomyces spp, clostridium spp)
- Gram-negative aerobic bacilli (enteric rods, proteus spp, pseudomonas aeruginosa, citrobacter diversus, and hemophilus spp.)

Clinical findings

- Initially, there are non-specific symptoms, i.e. low-grade fever, headache, and lethargy.

- Progressively, patient develops vomiting, severe headache, seizures, papilledema, focal neurologic signs (hemiparesis), and coma.
- In case of cerebellar abscess, there is nystagmus, ipsilateral ataxia and dysmetria, vomiting, and headache.
- Shock and death may occur if the abscess ruptures into the ventricular cavity.

Diagnosis

- **White blood cell (WBC) count** may be normal or increased.
- **Blood culture** is positive in about 10% of cases.
- **CSF examination:** Total cells and protein may be normal or slightly increased. Glucose may be slightly low. Lumbar puncture is contraindicated in a suspected case of brain abscess due to the risk of herniation of the cerebellar tonsils.
- **Brain scan** shows an area of enhancement due to disruption of the blood-brain barrier.
- **CT scan and MRI:** On contrast CT, an abscess cavity shows a ring-enhancing lesion. It is a parenchymal low-density lesion. MRI also shows an abscess capsule and there is increased signal intensity.
- **EEG** shows focal slowing.

Treatment

Antibiotics

- A combination of vancomycin, a third-generation cephalosporin and metronidazole is given.
- When cyanotic congenital heart disease is the predisposing factor, ampicillin-sulbactam alone or a third-generation cephalosporin plus metronidazole may be used.
- Antibiotics should be changed according to culture and sensitivity results.
- Abscesses secondary to an infected ventriculoperitoneal shunt may be treated with vancomycin and ceftazidime.
- In immunocompromised patient, amphotericin B is given along with broad-spectrum antibiotics.
- Duration of antibiotic therapy is usually 3–4 weeks and depends on the response of treatment and suspected organism.

Surgery

- If an encapsulated abscess is causing a mass effect or raised intracranial pressure, it is treated with aspiration along with antibiotics.
- Surgery is indicated if:
  - Gas is present in the abscess
  - It is multi-loculated
  - It is located in the posterior fossa
  - A fungus is identified

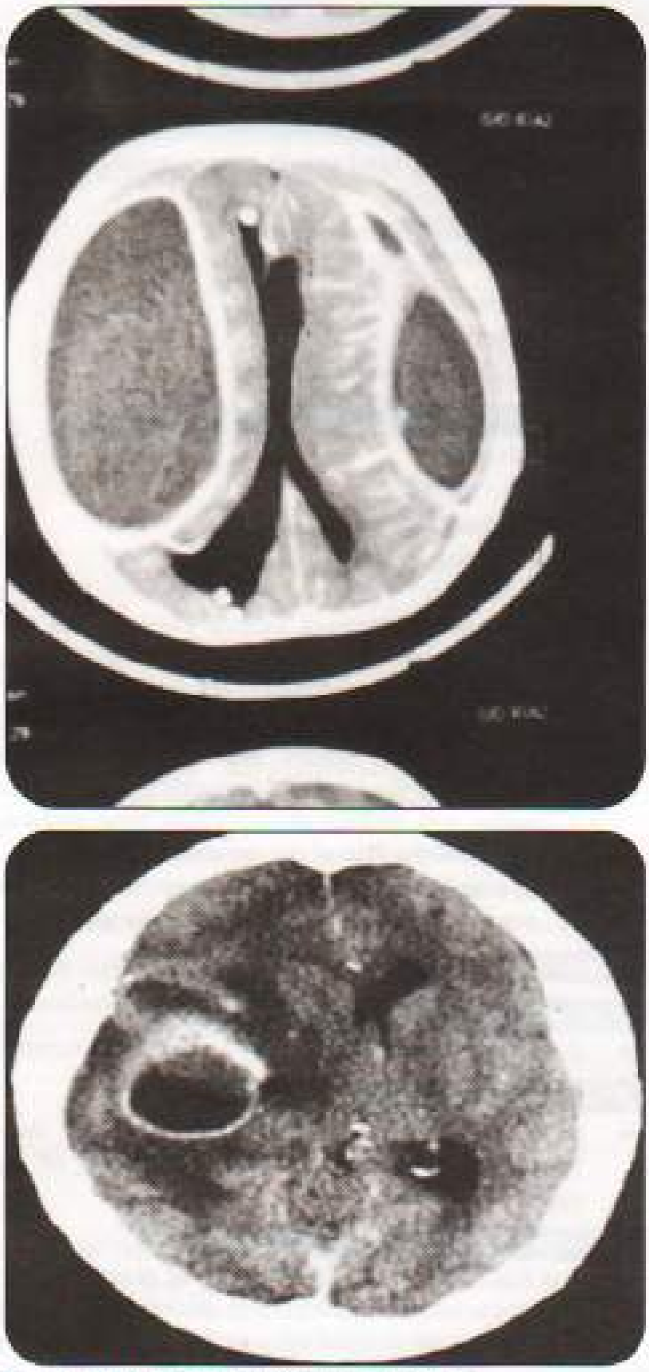


Figure 14.13: CT scan showing brain abscess.

Prognosis

- Factors associated with high mortality are:
  - Multiple abscesses
  - Coma
  - Lack of CT scan facilities
- Long-term sequelae are:
  - Hemiparesis
  - Seizures
  - Hydrocephalus
  - Cranial nerve palsies
  - Behavior and learning problems

PEDIATRIC STROKE

CASE

A 2-year-old child presents with ***suddenonset of right-sided weakness***. He is fully vaccinated. There is no fever.

- Commonly, hemiplegia occurs due to Space Occupying Lesion (SOL) or vascular disorders.

Incidence

- Incidence of hemiplegia due to cerebrovascular disorder (stroke) is 3–8/100,000.
- Stroke may occur at any age but is more common between the ages of 1–5 years.
- Congenital cyanotic heart disease is the most common underlying systemic disorder predisposing to stroke.
- Stroke may be due to arterial and venous thrombosis, intracranial hemorrhage, or embolism.

Etiologic risk factors for stroke

- In about 50% of cases, cause is unknown.

Cardiac disorders

- Cyanotic heart disease
- Valvular disease (rheumatic, endocarditis)
- Cardiomyopathy
- Cardiac dysrhytmia

Vascular occlusive disease

- Vasculitis (meningitis, SLE, polyarteritis nodosa)
- Diabetes mellitus
- Nephrotic syndrome
- Systemic hypertension
- Dural sinus and cerebral venous thrombosis (meningitis, hyperviscosity, hypovolemia)
- Arterial trauma (carotid dissection)
- Moyamoya disease (basal arterial occlusion with telangiectasia)

Hematologic disorders

- Coagulation defects (hemophilia, vitamin K deficiency)
- Polycythemia
- Thrombocytopenic purpura
- Hemoglobinopathies (sickle cell disease)
- Hypercoagulable states (SLE, antithrombin III deficiency, protein C and S deficiencies)
- Leukemia

Intracranial vascular anomalies

- Arterio-venous malformation
- Arterial aneurysm

Clinical assessment

- History must establish the presence of any relevant chronic illness e.g. congenital heart disease.
- There may be a recent history of trauma, or infectious disease.
- A family or past medical history of migraine or epilepsy is important.
- It is important to ask the mode of onset of the deficit and the presence of associated symptoms, e.g. in intracranial hemorrhage, there is sudden onset of headache rapidly leading to hemiplegia.
- Physical examination may reveal signs of a generalized bleeding disorder, retinal hemorrhages, trauma or local or systemic infection. Cardiovascular assessment including blood pressure measurement is important.
- Detailed neurologic examination may establish the likely vessel of occlusion, e.g. contralateral hemiparesis with legs affected more than arms occurs in occlusion of the anterior cerebral artery. On cranial auscultation, there may be a bruit associated with an arterio-venous malformation.

Clinical findings

- There is acute onset of unilateral weakness, sensory disturbances, dysarthria, and dysphasia.
- Acute hemiplegia may develop over a period of minutes, but sometimes progresses over several hours.
- There is depressed level of consciousness in a case with bilateral hemiparesis. There may be disturbances of mood and behavior. Focal or multifocal seizures may be present.

HHE syndrome

- This is a combination of hemiplegia, hemiconvulsion, and chronic epilepsy.

Diagnosis

- Complete blood count, ESR, blood culture.
- Coagulation studies to exclude bleeding disorders.
- CSF examination is indicated in patients with fever, neck stiffness, and consciousness disturbances to exclude the diagnosis of intracranial infection. Lumbar puncture is performed only if raised intracranial pressure has been excluded and is contraindicated in a suspected case of SOL or brain abscess.
- CT and MRI scans of the brain define the extent of cerebral involvement with ischemia or hemorrhage. CT scan may be normal within the first few hours of an ischemic stroke and may be repeated after some hours. Early CT scan is helpful in a case of intracranial hemorrhage.
- Brain scan is helpful in focal encephalitis, cerebritis, cerebral abscess, and infarction.
- EEG in a case of seizures.
- Cerebral angiography is indicated in case of cerebral arteritis.
- ECG and echocardiography are helpful in a patient with some cardiac lesion.
- Lipid studies if no cause is found and there is a family history of stroke.

Differential diagnosis

- Hypoglycemia
- Prolonged focal seizures
- A prolonged postictal paresis (Todd's paralysis)
- Migraine
- Neurodegenerative disorder (e.g. adrenoleukodystrophy)
- Status epilepticus

Management

- Give support for pulmonary, cardiovascular, and renal function.
- Give appropriate fluid and electrolyte infusions.
- There should be careful monitoring of blood pressure, heart rate and rhythm.
- Specific management depends on the underlying predisposing factor.
- Heparin is given in a case of emboli or DIC.
- Long term management includes:
    - Intensive rehabilitation efforts
    - Anticonvulsant treatment
    - Speech therapy

Prognosis

- It depends on the underlying cause of the stroke and the vascular area of brain involved. Early treatment also improves prognosis.
- Seizures may occur in 30–50% of cases of stroke.
- Chronic problems with learning, behavior, and activity are common.

CEREBRAL PALSY (CP)

CASE

A 3-year-old infant was ***born prematurely*** and had required ventilation for respiratory distress. He is now ***unable to walk or talk***. There is ***increased tone*** in the legs. Reflexes are increased in the arms and legs. He positions his legs in a ***scissoring posture*** when held by the axillae. He has normal cognitive development. He has PVL (***periventricular leukomalacia***) on MRI.

Definition

- Cerebral palsy is defined as a non-progressive, permanent disorder of posture and movement.
- It is a static encephalopathy.
- It is a disorder involving the motor areas, which results from events before birth or during the first year of life when the brain is immature.
- The term is rarely applied to brain lesions incurred after the age of two years.

Incidence

- The incidence of cerebral palsy is about 7:1000 live births.
- Prevalence is about 500 cases per 100,000 population.

Etiology

- No definite etiologic diagnosis is possible in over 50% of cases.
- Insult to the brain may occur prenatally, perinatally, or postnatally.
- Less than 10% of children with CP have evidence of intrapartum asphyxia.
- Although prematurity is the most common antecedent of CP, the majority of infants who develop this disorder are full-term.
- The lower the birth weight, the higher the incidence of CP.
- Preterm infants with intraventricular hemorrhage are at the greatest risk for developing CP. The major lesions that contribute to CP in preterm infants are intracerebral hemorrhage and periventricular leukomalacia (PVL).
- The best predictor of CP is the presence of echodensities in the peri-ventricular white matter that develops into cysts. There is 90–95% chance of developing a spastic diplegia if the cysts are more than 3 mm in diameter.
- The main causes can be classified according to the time they occur.

Intrauterine

Abnormalities of intrauterine environment include:

- Bleeding.
- Infections such as rubella and toxoplasmosis.
- Thromboembolic phenomena.
- Congenital malformations: Disorders of neuronal migration (polymicrogyria). Schizencephaly (double porencephalies).
- Massive irradiation.

Peri-natal and postnatal

Perinatal factors are the commonest cause and these include:

- Birth trauma
- Intracerebral hemorrhage, cerebral infarction
- Birth asphyxia, hypoxic ischemic encephalopathy
- Hypoglycemia
- Kernicterus
- Acidosis

Infancy

Illness of infancy account for 10% of cerebral palsy e.g:

- Meningitis
- Encephalitis
- Trauma
- Vascular accidents

Pathology

- In severe cases there is widespread cerebral atrophy with cavity formation in sub-cortical white matter.
- There is atrophy of basal ganglia when rigidity and extrapyramidal movements are present.

- With hemiplegia, there is atrophy and gliosis of the opposite cerebral hemisphere supplied by the middle cerebral artery.

Classification

- Classification is based on predominant motor deficit.

Table 14.17: Different forms of cerebral palsy (approx % of CP):

Different forms of cerebral palsy (approx % of CP):	
Spastic diplegia	(35%).
Spastic quadriplegia	(20%).
Spastic hemiplegia	(25%).
Extrapyramidal (athetoid, dyskinetic) CP	(15%).
Atonic CP.	
Mixed CP	

Spastic forms

- It includes about 75% of cases. Spastic diplegia comprises the largest number of CP patients.

Quadriplegia

- The four extremities are equally involved.
- It is the most severe form of CP due to the severe motor impairment of all four limbs.
- It is associated with low birth weight and severe asphyxial insults.
- Seizures and mental retardation are much more common in spastic quadriplegia.
- Due to supra-nuclear bulbar palsies, there are swallowing difficulties.
- There is spasticity in all four limbs with decreased spontaneous movements, brisk tendon reflexes, and positive Babinski sign.
- Due to extreme spasticity, there are flexion contractures of the knees and elbows.
- Speech and visual abnormalities are common.

Diplegia

- Legs are involved more than arms.
- In severe forms, there is excessive adduction of the hips (a scissoring posture of the lower limbs).
- There are brisk tendon reflexes, positive Babinski sign and ankle clonus.
- Walking is delayed. Child walks on tiptoes.
- Lower limbs have impaired growth due to disuse atrophy.
- Intellectual development is normal.
- Chances to develop seizures are minimal.
- Learning disabilities and language problems are present.
- Most babies were born premature and low birth weight with or without evidence of periventricular leukomalacia (in the area where fibers innervating the lower limbs pass through the internal capsule).
- Diplegia is becoming the most common type of spastic CP as more preterm infants survive.

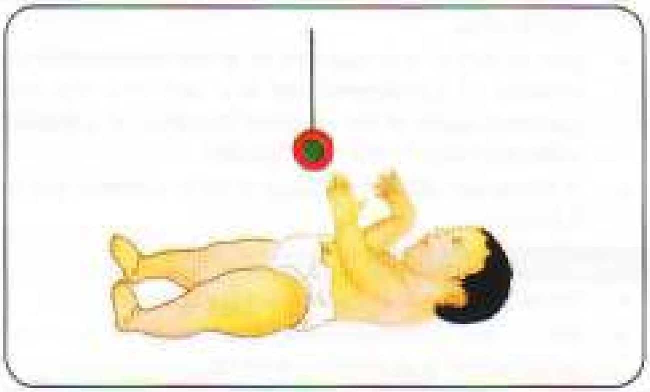


Figure 14.14: Hand preference in child with cerebral palsy.

Hemiplegia

- Infants with spastic hemiplegia have decreased spontaneous movements on the affected side.

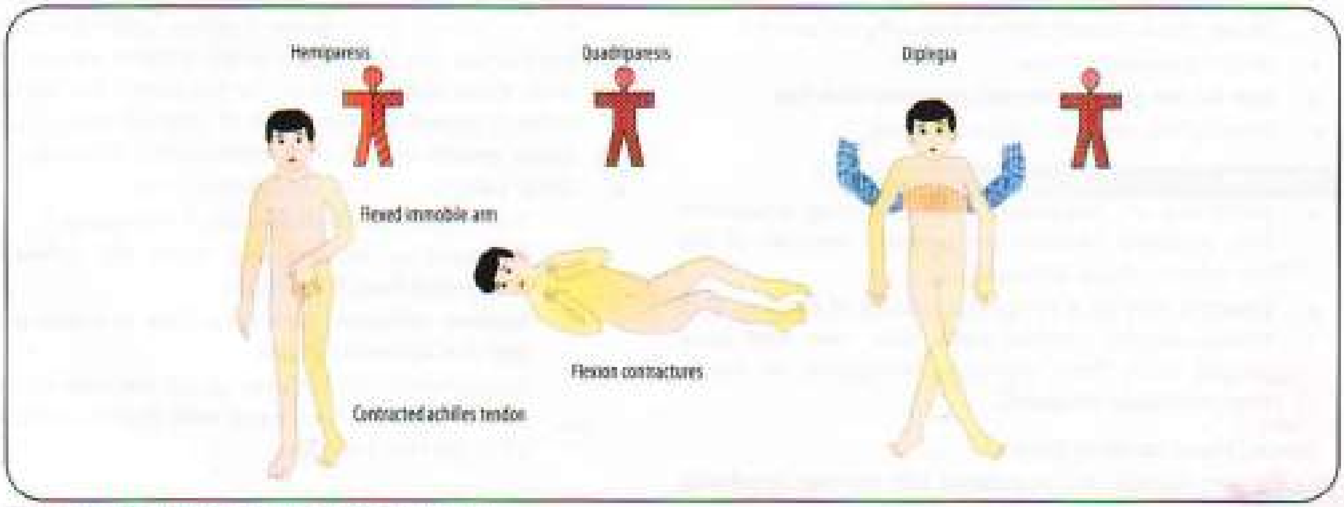


Figure 14.15: Different types of cerebral palsy.

- It may be due to cerebrovascular insults, such as embolic phenomena or vascular malformations.
- They show hand preference at a very early age.
- Arm is often more involved than the leg.
- Difficulty in hand movements is apparent by 1 year of age.
- Walking may be delayed until 18–24 months.
- Gait is usually circumductive.
- There may be growth arrest of the affected limbs.
- Affected extremities are spastic.
- Due to this spasticity, child walks on tiptoes.
- Deep tendon reflexes are brisk with positive Babinski sign and ankle clonus.
- Cognitive function may be spared because only one side of the brain is involved.

Monoplegia

- One extremity only involved.

Extrapyramidal form

- It has been closely associated with the development of kernicterus.
- Due to better management of blood incompatibilities, chances of kernicterus are less and now the most common cause of the athetoid-dystonic CP is hypoxic-ischemic injury to the basal ganglia.
- It comprises 20% of all cerebral palsy patients and has 2 forms:

Choreoathetosis

- There are irregular, involuntary movements.
- Infants are characteristically hypotonic and have poor head control and marked head lag.
- There are feeding difficulties, tongue thrust and drooling.
- Athetoid movements usually become evident after 1 year of age due to hypermyelination of the basal ganglia (status marmoratus).
- Due to the involvement of the oro-pharyngeal muscles, speech is typically affected.
- Upper motor neuron signs are usually not present.
- Seizures are uncommon.
- Mostly, the patients are not mentally retarded.
- Hearing impairment is more common.

Dystonia

- Dystonia is an involuntary, slow, twisting movement that primarily involves the proximal muscles of the extremities, trunk, and neck.
- Dystonia may be a prominent feature of children with extrapyramidal cerebral palsy who have had basal ganglia injury from asphyxia, kernicterus, or insults from metabolic disorders.

Atonic/ataxic cerebral palsy

- Atonic diplegia: It is associated with marked hypotonia, brisk reflexes, and severe cognitive delays.
- Congential cerebellar ataxia: There is incoordination, and intention tremors. Hydrocephalus often is present in ataxic-spastic disorders. Genetic factors have been implicated in the pure ataxic CP.

Mixed form of CP

- Some children have mixed disorders incorporating features of the above types.
- It is due to combinations of insults to multiple cerebral areas.
- It is associated with more complications (sensory deficits, seizures, cognitive and perceptual impairment).

Associated deficits

Seizures

- Seizures afflict about 60% of children with cerebral and about one third with movement disorders.

Mental retardation

- Mental retardation is present in 25–50% cases of cerebral palsy but it is not an essential feature.

Sensory and speech deficits

- The impairment of speech, vision, hearing and perceptual functions is frequently present in varying degrees and combinations.

Clinical findings

- It is important to realize that although the brain lesion is fixed and non-progressive, the disorder it causes varies in the early years as different movement patterns are acquired. Thus an affected infant is often floppy and hypotonic up to the age of 6 months and then becomes hypertonic.
- Most primitive reflexes persist beyond their normal age e.g. persistence of Moro reflex beyond the age of 3 months is a good cause for suspicion of cerebral palsy. Undue persistence of stepping reflex more than 6 weeks is another common finding in CP. Landau reflex is also of value. It is seen normally in infants between the age of 3 months and 1.5 years. When the baby is held in the air in the prone position with examiner's hand under the lower part of the anterior wall of the chest there is extension of the hip joints. The Landau reflex is absent in most cases of cerebral palsy, lower motor neuron disease and severe mental deficiency.
- Other valuable signs of cerebral palsy are:
    - Poverty of movement and facial expression
    - Extended or crossed legs when the infant is suspended from the armpits
    - Marked adductor spasm resulting in crossing of legs and scissoring of gait
    - Exaggerated deep reflexes and in the upper limbs persistently clenched hand with thumb adducted after the first 3 months

- At a later age the child may walk on his toes with typical spastic gait and the planter responses are extensor but abdominal reflexes are present.
- The typical spastic child exhibits muscular hypertonicity of the clasp knife type that may eventually end in contractures.
- In early infancy child may appear floppy, although tendon jerks are abnormally increased.
- Athetosis may only become obvious after the age of two years but they show delayed motor development during infancy.
- Ataxia may be difficult to delineate in the presence of spasticity or hyperkinetic movements.
- Microcephaly (head circumstance below 2 SD) is present in about 25% of spastic quadri and diplegics. A smaller hand or foot, when coupled with mild weakness on muscle testing or hyperreflexia often justifies the diagnosis of mild cerebral palsy.
- Delay in speech may be due to spasticity or athetosis of the tongue or to high tone deafness.

Diagnosis

- Diagnosis is mostly clinical based on careful history and physical examination to exclude any progressive CNS disorder (degenerative brain disease, spinal cord tumor, or muscular dystrophies).
- Any infant whose motor development has been delayed must be suspected a case of CP.
- Diagnosis is very difficult before 6 months of age because during early infancy abnormalities of tone, reflexes, and involuntary movements are not appreciated. Much of the movements in infants are reflex in origin and are not under voluntary motor cortical control.
- Clinical picture is only evident when cerebral cortex matures.
- One should be highly suspicious of the presence of CP if there is a motor delay but evidence of normal cognitive development, but about 50% of CP patients may also be mentally retarded.
- To locate the structural lesions or associated congenital anomalies, EEG or CT scan may be helpful.
- As CP may be associated with hearing and vision impairment, tests of hearing and vision are important.

Differential diagnosis

- **Leukodystrophy:** In leukodystrophy spinal fluid protein is elevated but not in cerebral palsy.
- **Hydrocephalus/subdural effusion:** In these head size is large and signs of increased intracranial pressure are present.
- **Brain tumor:** In this the disability is always progressive and signs of intracranial pressure are usually present.
- **Spinal cord lesions:** In these spas-ticity and weakness are limited to the muscle groups below the neck.
- **Muscular dystrophy:** Heel cord contractures and weakness occur in both but spasticity is absent in muscular dystrophy and tendon reflexes are normal or reduced and CPK is increased.
- **Werdnig Hoffmann and benign congenital hypotonia-atonic diplegia:** In these, there is no mental deficit while in atonic diplegia tendon reflexes are well preserved.
- **Progressive CNS disorder:** There are some differentiating points about a progressive CNS disorder:
    - Regression (child loses previously acquired skills and milestones)
    - Consanguinity
    - Congenital skeletal anomalies such as pes cavus or scoliosis
    - Neuro-cutaneous stigmata
- The presence of more than one child with motor deficit in the same family should always alert the physician to the likelihood of a disease other than cerebral palsy.

Management and prevention

- The treatment of child with cerebral palsy consists of:
    - Physical and occupational therapy
    - Control of seizures
    - Stretching exercise
    - Surgical procedures to prevent contractures
- The aim of treating the physical disability is to improve function and to prevent secondary complications of the musculo-skeletal system.
- Parents should be taught how to handle their child in daily activities.
- Family support is essential for emotional growth to manage the child.
- Exercises are advised to prevent the contractures.
- Tight Achilles tendon is a common problem and in case of contractures requires surgical treatment (adductor tenotomy, psoas transfer, and release).
- Diazepam, baclofen (Lioresal), and dantrolene may reduce spasticity but drowsiness, lethergy and poor handling of salivary secretions are the limiting factors.
- Anticholinergic Trihexyphenidyl (Hexidyl, Pacitane) is also used.
- Patients with athetosis may get benefit by using levodopa.
- Children with dystonia may respond to carbamazepine.
- Hearing, vision, learning, and mental disorders are accordingly managed.
- Prevention of cerebral palsy can be accomplished by prevention of kernicterus, meticulous care of low birth weight infants and prompt therapy of apneic episodes.

Prognosis

- It depends on the extent of disability and the type and intensity of rehabilitation efforts.
- Physical and intellectual abilities are the primary determinants of functional potential.

MENTAL RETARDATION

CASE

A 6-year-old male child is a known case of tuberous sclerosis. He has history of recurrent attacks of ***convulsion*** since 4 month of age. He has ***autistic behavior*** and severe degree of ***mental retardation***.

Definition

- It is defined as impairment in intelligence from early life and inadequate mental development throughout the growth period.
- Mental retardation is defined statistically as cognitive performance that is 2 standard deviation below the mean (below the 3rd percentile) of the general population.
- Intelligence is defined as ability for abstract thinking, visual and auditory memory, causal reasoning, verbal expression, manipulative capacities and spatial comprehension.
- Intelligence is measured in terms of intelligence quotient (IQ).

$$IQ = \frac{\text{Mental age}}{\text{Chronological Age}} \times 100$$

Prevalence

- The prevalence of mental retardation in Pakistan is 3.92%.
- There is no known cause found in 1/3rd cases of mental retardation.
- There may be some cause found in 2/3rd cases of mental retardation.

Classification

- Intelligence quotient (IQ) is used to classify subnormal into following four types:

Mildly retarded: (Educatable)

- Children with IQ between 52–67 are considered mildly retarded and are educatable.
- They comprise 85–90% of the total and are recognized during early school years, as they are unable to cope with normal schools.

Moderately retarded: (Trainable)

- They have IQ between 36–51 and are considered trainable and comprise 5-10% of mentally retarded.
- They are capable of their own physical self-care and can make adequate social adjustment.

Severely retarded: (Non-trainable)

- Their IQ is between 20–35 and comprises 5% of the total.
- They are recognized during infancy and have multiple physical disabilities and usually depend on other for most of their care.

Profoundly retarded

- They are severely handicapped and their IQ is below 20.

Etiology

- No identifiable cause can be found in 65–75% of retarded children but mostly they are found in families of low intellect and poor social background.
- Important causes are mentioned in the table given below.

Clinical findings

- In gross congenital abnormalities, the mentally handicapped child is likely to present with slowness in achieving skills.
- He will be slow in all four fields of development, i.e. posture and movement, vision and manipulation, hearing and speech, and social behavior.
- The child is found to be slow from early life, smiling at 3 or more months of life, primitive reflexes may persist beyond 6 months of age or child continues to play with his hands after the age of 6 months.

Table 14:18: Causes of certarded in clinical findings in mentally retarded children.

Prenatal causes	• Chromosomal disorders (e.g Down syndrome) • TORCHS infections • Congenital primary hypothyroidism • Family history of mental retardation • Malformations of brain
Perinatal causes	• Prematurity • Hypoxic-ischemic encephalopathy • Birth trauma • Intracranial hemorrhage
Postnatal causes	• Birth trauma • Intraventricular hemorrhages • Bilirubin encephalopathy • Hypoglycemia • Bacterial meningitis, sepsis • Viral encephalitis
Structural defects	• Microcephaly • Hydrocephalus • Neural tube defects
Infections	• Post-encephalitic • Post-meningitic • Subacute Sclerosing Panencephalitis (SSPE)

Chromosomal disorders	• Down syndrome • Turner's syndrome • Cri-du-chat • Fragile-X syndrome
Environmental factors	• Psychosocial deprivation • Nutritional deprivation • Cranial trauma
Genetic/Metabolic defects	• Cretinism • Muco-poly-saccharidosis • Leukodystrophy • Galactosemia • Phenylketonuria
Unknown causes	

History

- Complaints of the parents about the mental status of the baby
- Pre-natal, peri-natal, and post-natal history
- Developmental history
- Any previous illness, e.g. meningitis, head trauma, etc.
- Family history of mental retardation
- Social history, parental education
- Consanguinity
- Child abuse or neglect

Examination

General physical examination

- Growth parameters especially head circumference
- Dysmorphic features or congenital malformations

CNS examination

- Complete CNS examination especially motor system

Table 14.19: The following delays (~ 30% or more) are definitely abnormal and always should prompt an evaluation for mental retardation.

The following delays (~ 30% or more) are definitely abnormal and always should prompt an evaluation for mental retardation.
• Failure to turn to a voice by 6 months. • Failure to babble by 9 months. • Failure to orient to name at 13 months. • Failure to point to request or comment by 18 months. • Failure to follow a simple command without a gesture by 18 months. • Failure to use 10 to 25 single words by 24 months. • Failure to speak in two-word phrases by 26 months. • Failure to speak in three-word sentences by 36 months. • Unintelligible speech in a child older than 36 months. • Regression in language skills at any age.

Development assessment

Eyes

Cataract

- Congenital rubella
- Galactosemia
- Hypoparathyroidism
- Myotonia

Retinopathy

- Congenital rubella
- Toxoplasmosis
- Laurence-Moon-Biedle syndrome

Lens dislocation

- Marfan's syndrome
- Homocystinuria

Heart

AV canal defect

- Trisomy 21 (Down syndrome)
- Patent ductus arteriosus
- Congenital rubella

Coarctation of aorta

- Turner syndrome

Supra-valvular aortic stenosis

- William syndrome

Liver

Hepatosplenomegaly

- Mucopolysaccharidosis
- Glycogenosis (type I and III)
- Galactosemia
- TORCHS infection

Skin

Café-au-lait spots

- Neurofibromatosis
- Tuberous sclerosis

Port-wine stain

- Sturge-Weber syndrome

Hands

- There may be polydactyly or syndactyly or large hands (Sotos syndrome) or broad thumbs (Rubinstein-Taybi syndrome).
- Simian creases are present in Down's syndrome, Cornelia-Delange and Smith-Lemli-Optiz syndrome.

Gonads

Hypogonadism.

- Prader-Willli syndrome (with obesity)
- Smith-Lemli-Optiz syndrome

Diagnosis

- History and physical examination may point to a likely cause.
- The risk factors in history are prematurity, complications of pregnancy and labour, history of birth

asphyxia, deep jaundice in the newborn period, convulsions, maternal rubella or family history of mental deficiency.

- Following investigations may be helpful.
  - T_4, TSH for hypothyroidism
  - Serology for TORCHS infection
  - Serum calcium for pseudo-hypopara-thyroidism
  - Serum/urinary aminoacids for aminoaciduria
  - Serum/urine organic acids for organic aciduria
  - Urine heparan/dermatan sulphate for mucopolysaccharidosis
  - X-ray skull for calcifications in TORCHS infection
  - CT scan brain for malformations
  - WBC enzymes for degenerative brain disorders
  - Chromosomal analysis for chromosomal disorders
  - Ophthalmic examination for retinopathy
  - Audiometery.
  - EEG (Electroencephalogram)

Management

- A few causes of mental subnormality are amenable to treatment.
- Specific causes if any should be treated, e.g. hypothyroidism, phenylketon-uria, etc.
- Routine medical care is essential because these children are more susceptible to infection and accidents.
- Parents should be made to understand the child's condition, its needs and prognosis.
- Genetic counseling should be provided to the parents if the cause is known and they should refrain from bearing further children.
- Less than 1% of mentally retarded need institutionalization, if the retarded child's presence in the family is causing significant hardship, to provide respite to the family from the stress of everyday care of the child, or they may help in modifying some types of behavior.

MICROCEPHALY

CASE

A 2-month-girl presents with failure to thrive. She weighs 2.7 kg, length is 49 cm and head circumference measures 34 cm (microcephaly). Neurologic examination reveals poor head control, and brisk deep tendon reflexes. CT of the head reveals calcifications. Cytomegalovirus screen is positive.

- A congenital anomaly of the central nervous system (CNS) where the head circumference is more than 3 standard deviations below the mean for age and sex.
- Head circumference reflects brain volume, with a small skull usually reflecting a small brain.
- Furthermore, the smaller the head, the less likely that intelligence will be normal.
- Incidence of moderate-to-severe mental retardation among infants who have a head circumference from 2 to 3 standard deviations (SD) below the mean is 33%, while among infants who have a head circumference more than 3 SD below the mean, the incidence is 62%.
- However, microcephaly is not always associated with mental retardation; exceptions include familial small heads and growth retardation secondary to physiologic disturbances such as malabsorption or congenital heart disease.
- Head circumference differs slightly between male and female infants at birth, with mean of 35 cm and 34 cm, respectively.
- At birth, the brain has achieved 25% and at 1 year of age about 75% of its adult volume.
- During the first 3 months of life, the head circumference should grow at a rate of 2 cm/month, from 4 to 6 months of life at 1 cm/month, and from 6 to 12 months at 0.5 cm/month. This growth pattern results in a mean head circumference of about 46 cm at 1 year of age.
- Age of onset: microcephaly at birth is usually genetic and after first 2 years of life is usually non-genetic.
- In congenital microcephaly, the forebrain is affected most severely, leading to characteristic features that include a sloping forehead and a small anterior fontanel.
- In acquired microcephaly, the infant's head circumference is normal at birth and their microcephaly (resulting from postnatal impairment of brain growth), becomes apparent after several months.

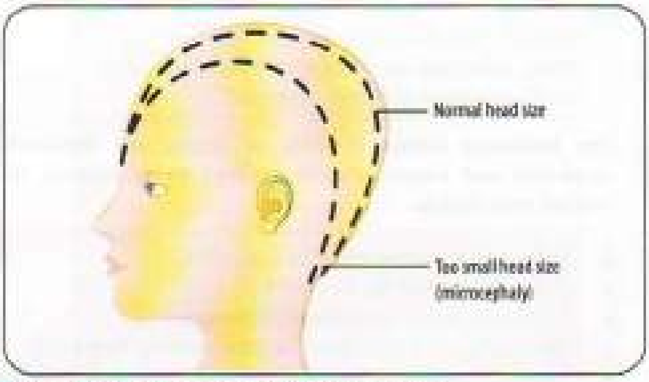

Normal head size
Too small head size (microcephaly)

Figure 14.16: Illustration: Microcephaly.

Etiology

Primary (Genetic)

- Autosomal recessive (Familial)
- Autosomal dominant
- Syndromes
  - Aicardi Syndrome
  - Prader-Willi syndrome

    - Beckwith-Wiedemann syndrome
    - Bloom Syndrome
    - Cri-du-chat (5p-)
    - Trisomy 21, Trisomy 18, Trisomy 13

Secondary (Nongenetic)

- Congenital CNS anomalies
    - Agenesis of the cerebellar vermis
    - Agenesis of the corpus callosum
    - Craniosynostosis
    - Encephalocele
    - Holoprosencephaly
    - Lissencephaly
    - Macrogyria
    - Porencephaly
    - Schizencephaly
- Congenital infections (CMV, rubella, toxoplasmosis, varicella)
- Hypoxic-ischemic encephalopathy
- Infections (encephalitis, meningitis)
- Metabolic (maternal diabetes mellitus, maternal PKU, inborn errors of metabolism)
- Others (radiation, hyperthermia)

Pathogenesis

- Most often occurs as a result of a small brain (micrencephaly) but also due to a poorly growing skull (i.e. craniosynostosis). Micrencephaly may be due to:
    - Abnormal neuronal migration during fetal development
    - Heterotropias of neuronal cells
    - Cytoarchitectural derangements
- If insult to brain occurs beyond 2 years of age it is less likely to produce severe microcephaly.

Clinical findings

- Important points in history are:
    - Genetic or non-genetic
    - Family history (for genetic etiology)
    - Exposure to risk factors: radiation, infection, drugs, maternal diabetes mellitus or phenylketonuria
    - Significant fever during first 4–6 weeks of life
    - Hypoxic ischemic encephalopathy
    - Head circumference curve characteristics-if small at birth means in utero problems
    - Dysmorphic features
    - Seizures
    - Developmental delay
- More important, however, than a single head circumference measurement is the rate or pattern of head circumference through time.
- Look for dysmorphic features. These may be present in chromosomal diseases.
- In TORCHS infections, other typical abnormalities may be present, e.g. petechiae, hepatosplenomegaly, chorioretinitis, and intracranial calcifications.
- The fontanel may close earlier than expected, and sutures may be prominent.
- Microcephaly may be suspected in the full-term newborn and in infants up to 6 months of age whose chest circumference exceeds the head circumference (unless the child is very obese).

Diagnosis

- CT/MRI (for structural anomalies: cerebral/cerebellar atrophy, hydrocephaly, calcification, craniosynostosis)
- Serum (karyotype in chromosomal diseases, plasma for amino acids, serum ammonia, TORCH screen (toxoplasmosis, rubella, CMV, HSV), maternal blood for phenylketonuria.
- Urine (amino acids and organic acids in case of inborn errors of metabolism; urine culture for CMV).

Management

- Anticonvulsants
- Physiotherapy
- Dietary management for failure to thrive
- Genetic counseling

Prognosis

- The prognosis for infants who have microcephaly varies significantly, depending on the underlying cause.
- Those whose microcephaly is part of a wider pattern of malformation, as with trisomies, and with TORCHS infection have a poor prognosis.
- In some situations, however, damage to the brain and subsequent microcephaly can be minimized or even prevented. Prevention of birth asphyxia, aggressive management of phenylketonuria, and early identification of hypothyroidism with appropriate replacement therapy all can improve the prognosis of an affected neonate.

ATAXIA

- Ataxia is defined as the inability to make accurate, smooth and coordinated movements. It is usually due to a dysfunction of the cerebellar pathways.
- The usual symptoms of ataxia are:
    - A broad-based, unsteady gait (truncal ataxia).
    - An intention tremor or dysmetria(over or undershooting of the target due to abnormal distance perception).
- Drug intoxicationis the most common cause of acute ataxia among children.
- Postinfectious acute cerebellar ataxia may occur 1 to 3 weeks following varicella, infectious mononucleosis, mild respiratory or gastrointestinal viral illnesses, or other infections.

- Brain tumorsare the second most common neoplasm in children. About 50% arise from within the posterior fossa. Tumors that arise in the posterior fossa or brainstem produce progressive ataxia with headache.

Etiology

Acute ataxia

- Acute cerebellar ataxia due to viral infections (varicella, measles, mumps, herpes simplex virus)
- Meningitis, encephalitis, cerebellar abscess
- Over dosage of drugs such as benzodiazepines, carbamazepine, phenytoin, phenobarbitone
- Lead intoxication
- Posterior fossa tumors
- Migraine
- Occult neuroblastoma
- Epilepsy (postictal state)
- Guillain Barre syndrome

Chronic ataxia

- Ataxic cerebral palsy
- Leucodystrophies
- Wilson's disease
- Ataxia-telangiectasia

ACUTE CEREBELLAR ATAXIA

> CASE
>
> **Acute cerebellar ataxia preceded by a viral illness:** A 2-year-old girl presents with acute onset of ***truncal ataxia*** with vomiting, nystagmus, and dysarthria. She is afebrile and has ***no nuchal rigidity***. There is ***past history of sore throat*** with blisters on palate 2 weeks ago.

- It occurs most commonly in children aged 2–6 years.
- There is rapid onset of symptoms. Commonly, there is a preceding viral respiratory tract infection.
- Ataxia may be associated with slurred speech, hypotonia, tremors of the extremities, and horizontal nystagmus.
- Child is frequently irritable. There may be vomiting.
- There are no signs of raised intracranial pressure. Sensory and reflex testing is normal.
- CSF examination is normal with slight lymphocytosis.
- CT scan is normal.
- MRI show cerebellar postinfectious demyelination.
- Treatment is supportive as this is a self-limiting disease without sequelae. Recovery occurs within 6–8 weeks.
- Monitor for malignancy.

ATAXIA TELANGIECTASIA

- Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.
- Ataxia-telangiectasia progressively destroys part of the motor control area of the brain, leading to a lack of balance and coordination.
- Further detail is given in chapter about immunologic disorders.

NEUROFIBROMATOSIS (NF)

> CASE
>
> A 6 months old infant is otherwise normal except having many ***café au lait spots*** on whole body. His father is a case of neurofibromatosis.

- Neurofibromatosis type 1 (NF1) or von Recklinghausen disease is an autosomal-dominant disorder.
- Incidence is approximately 1 in 3000.
- The cardinal features of neurofibromatosis are café au lait spots, axillary or inguinal freckling, cutaneous neurofibromas, and iris hamartomas (Lisch nodules).
- Café au lait spots are present in more than 90% of patients who have NF1.
- Type 1 NF is a genetic neuroectodermal disorder.
- 50% of cases are due to new mutations in *NF1* gene.
- Main clinical findings are:
  - Learning disabilities (40%)
  - Mental retardation (8%)
  - Strabismus or amblyopia (optic glioma)
  - Unexplained skin masses
  - Macrocephaly
  - Neurologic symptoms of spine or brain tumor
  - Hypertension
- Many asymptomatic patients are identified after a first-degree relative is diagnosed.
- Although patients with NF type 1 may have brain, spinal cord, and optic nerve tumors, auditory nerve tumors (acoustic neuromas) only occur in NF type 2.
- Plexiform neurofibromas are invasive. They grow rapidly during growth spurts. When present on face or limbs, they may cause significant hypertrophy of the underlying bony and soft tissues.

Diagnosis

Diagnostic criteria:

- >6 café au lait spots of >5 mm diameter (prepuberty) or >15 mm (postpuberty)
- >2 neurofibromas of any type or 1 plexiform neurofibroma
- Axillary or inguinal freckles
- Optic glioma (15% of patients)
- >2 Lisch nodules (iris hamartoma)
- Osseous lesions (sphenoid dysplasia, pseudarthroses, thinning of long bones)
- Affected first-degree relative

Differential diagnosis

- McCune-Albright syndrome (patients have larger café au lait spots)
- Watson syndrome
- Normal children frequently have one or two café au lait spots. A large single café au lait spot is usually innocent
- Café au lait spots are occasionally seen in tuberous sclerosis.
- Type 2 NF (patients have bilateral acoustic neuromas and no skin changes)
- Hyperpigmented skin macules can occur in Albright syndrome, Noonan syndrome, LEOPARD syndrome but usually easily differentiated.
- Familial café au lait spots
- Isolated non-syndromatic neurofibromas

Management

- No specific treatment is available for neurofibromatosis.
- Genetic counseling is important. This includes, genetic counseling of parents and screening examination of siblings.
- Early detection of treatable conditions or complications is indicated.
- Regular visual assessment is advised.
- Lifelong regular monitoring for brain and spinal tumors, hypertension, scoliosis and other orthopedic problems, optic glioma, acoustic neuroma, disfiguring skin masses, delayed puberty, emotional and psychiatric problems is required.
- Cognitive and psychological testing should be done early to maximize effectiveness of interventions.
- Neurofibromas causing cosmetic or functional problems can be removed surgically.

TUBEROUS SCLEROSIS

CASE

A 10-month-old girl presents with tonic-clonic ***seizures***. She has multiple small 1–2 cm oval, irregular ***hypopigmented macules*** on her trunk and extremities. CT scan brain shows ***cortical tubers*** in the cerebral cortex and multiple subependymal nodules in the lateral ventricles. EEG shows hypsarrhythmia. A renal ultrasound shows tumors in both kidneys.

- Tuberous sclerosis is an autosomal dominant disorder, is characterized by hamartomas in many organs, especially the brain, eyes, skin, kidneys, and heart.
- Tubers in the cerebral cortex are areas of dysplasia that are responsible for the symptoms of mental retardation and epilepsy.

Clinical findings

- Typical hypomelanotic macules (ash leaf macules)
- Sebaceous adenomas (facial area)
- Shagreen patches (lumbo-sacral area)
- Seizures
- Cognitive impairment (mental retardation)
- Retinal hemartomas
- Cardiac rhabdomyoma
- Intracranial calcifications (peri-ventricular)
- Renal cysts

Course of the disease

- Hypopigmented oval or irregularly shaped skin macules (ash leaf) at birth
- Cerebral sclerotic tubers present since birth (radiographically appear at 3–4 years)
- Myoclonic then grand mal seizures
- Adenoma sebaceum at 4–7 years of age

Differential diagnosis

- Facial rash may be confused with acne, acne rosacea, cystic acne.
- Intrauterine infection may cause intracranial calcification and seizures.
- Three or fewer ash leaf spots is normal.
- When café au lait spots are present, there may be some consideration of NF.
- Trauma may cause subungual fibroma.

Diagnosis

- Renal USG
- Head CT scan or MRI
- Echocardiogram
- CXR.
- Genetic testing for TSC1 and TSC2 mutations

Management

- Regular monitoring for complications
- Control seizures
- Skin lesions may require laser or dermabrasion
- Tumors must be treated
- Genetic counseling. Heterozygotes have a 50% chance of passing the condition to offspring
- Treatment of raised Intracranial Pressure (ICP)

STURGE-WEBER SYNDROME (SWS)

CASE

A 1 year old child presents with ***seizures*** since the age of 3 months. There is a ***port-wine stain*** on right side of face along the ophthalmic division of trigeminal nerve.

- Sturge-Weber syndrome is a sporadic (not inherited) vascular disorder (angiomas).
- It consists of a constellation of symptoms and signs including:
    - A facial capillary malformation (port-wine stain)

  - Abnormal blood vessels of the brain (leptomeningeal angioma)
  - Abnormal blood vessels of the eye leading to glaucoma
- Patients present with seizures, hemiparesis, stroke-like episodes, headaches, and developmental delay.
- About 1 in 50,000 newborns are affected with Sturge-Weber syndrome.

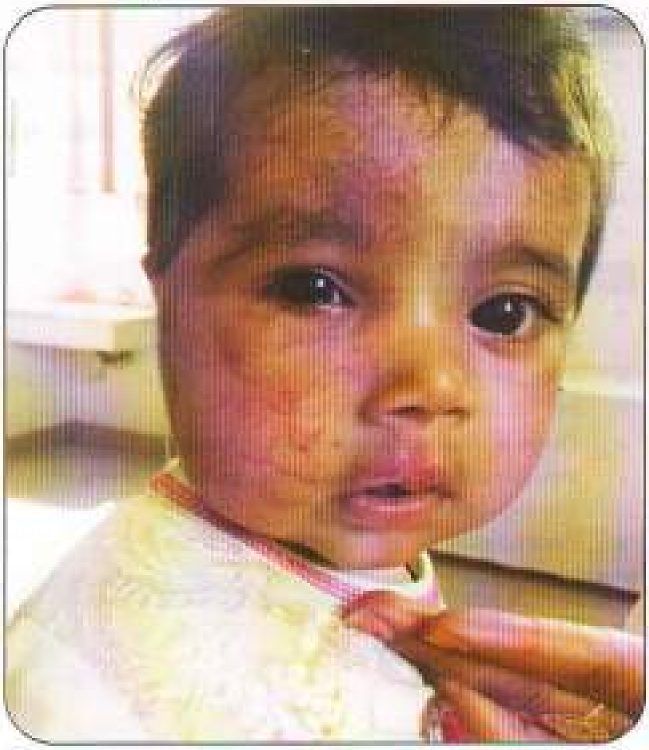


Figure 14.17: An infant with left-sided port-wine stain on upper face.

Clinical findings

- The facial port-wine stain is present at birth. It tends to be unilateral. It always involves the upper face and eyelid. Distribution involves the area supplied with the ophthalmic division of the trigeminal nerve.
- Not all children with facial port-wine stain have Sturge-Weber syndrome.
- Incidence of epilepsy in patients with Sturge-Weber syndrome is 75–90%. Seizures develop mostly in the first year of life.
- Seizures may become refractory to anticonvulsants and are associated with a slowly progressive hemiparesis.
- Intellectual disability or severe learning disabilities are present in at least 50% in later childhood. This may be due to intractable epilepsy and increasing cerebral atrophy.

Diagnosis

- MRI with contrast (demonstrate the leptomeningeal angioma, white matter abnormalities, cerebral atrophy).
- Calcifications can be seen best with a head CT scan.
- Ophthalmologic evaluation is needed for glaucoma.

Management

- Management of Sturge-Weber syndrome is symptomatic and multi-disciplinary.
- This includes:
  - Seizure control
  - Treatment of headaches
  - Prevention of stroke-like episodes
  - Monitoring of glaucoma
  - Laser therapy for the cutaneous capillary malformations
- If the seizures are refractory to anticonvulsant therapy (especially in infancy and the first 1–2 years) and arise from primarily one hemisphere, a hemispherectomy indicated.
- Because of the risk of glaucoma, regular measurement of intraocular pressure is indicated.
- Laser therapy often clears the port-wine stain, particularly if it is located on the forehead.

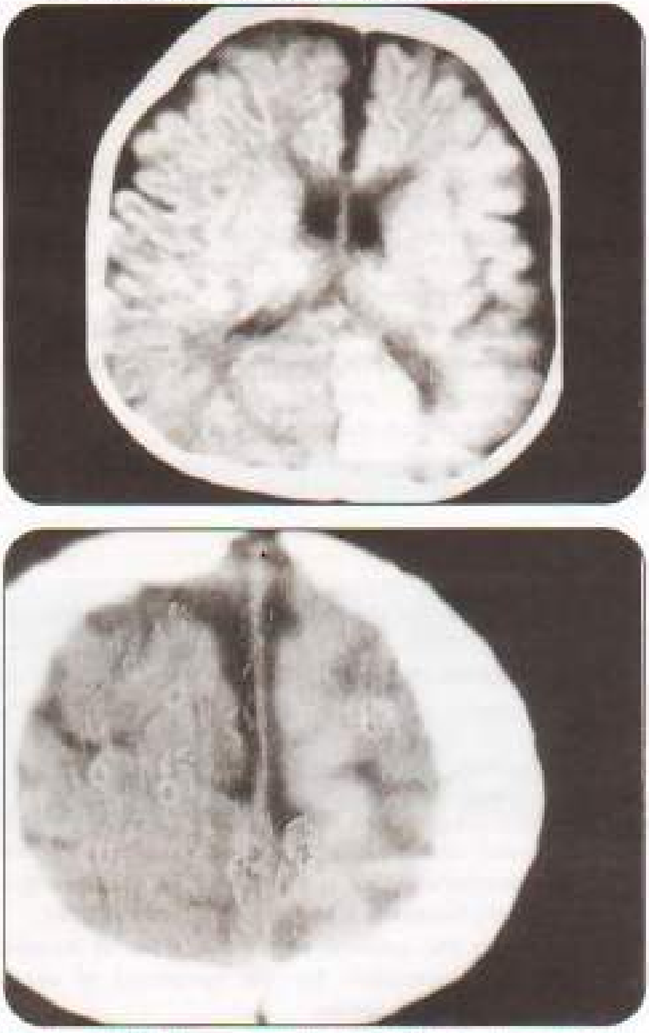


Figure 14.18: CT scan showing left-sided cerebral atrophy in Sturge-Weber syndrome.

MULTIPLE SCLEROSIS

CASE

A 12-year-old girl presents with ***ataxia*** for last 6 months. A brain MRI shows multiple 3 mm ***oval white lesions*** with poorly defined margins in the periventricular areas of the white matter.

Clinical findings

- Multiple white lesions in the CNS.
- Family history of multiple sclerosis may be present.
- Unilateral weakness with Upper Motor Neuron (UMN) signs.
- Sensory abnormalities, visual complaints, ataxia, paresthesia.

Differential diagnosis

- CNS vasculitis (SLE, polyarteritis nodosa)
- Acute demyelinating encephalomyelitis
- Small vessel infarcts
- Neurosyphilis
- Optic neuritis due to other causes
- Cerebellar ataxia of other causes
- Metastatic or primary brain tumor, spinal cord injury, tethered cord, transverse myelitis, or spinal syrinx
- Emotional/psychiatric problems

Management

- Suggested medical therapies are same as in adults
- Corticosteroids reduce inflammation and limit duration of relapse. High dose IV methyl-prednisolone is indicated
- Disease modifying interferon therapies (interferon–beta)
- ☐Interferon reduces relapse rate but side effects are significant
- Medications for muscle spasticity, depression, constipation, incontinence, and bladder spasticity may be needed
- Physical therapy
- Rehabilitative care
- Management of a neurogenic bladder

CHAPTER 15

Neuro-Muscular Disorders

DUCHENNE MUSCULAR DYSTROPHY

CASE

A 4-year-old boy presents ***difficulty in walking***. He rolled, sat, and first stood at essentially normal ages and first walked at 12 months of age. For the last several months, mother has noticed an increased inward curvature of the lower spine as he walks and difficulty in going upstairs. His gait has become more ***waddling*** in nature. He is clumsy and ***fell excessively***. Has normal mental development. On examination he has ***enlargement of his calves***. He has a ***positive Gower sign. Serum creatine kinase level*** is 9000 IU/L (***raised***). Diagnosis was confirmed by muscle biopsy.

- Duchenne Muscular Dystrophy(DMD) is the most common hereditary neuromuscular disease
- It is inherited X-linked recessive condition. About 30% of cases are new mutations.
- These patients do not produce dystrophin. Dystrophin is a protein localized to muscle cell membrane.
- Incidence is 1:3600 male births.
- Female carriers are usually asymptomatic.

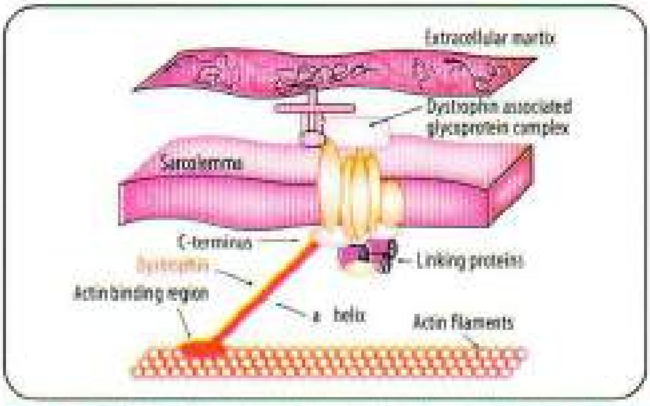


Figure 15.1 : Structure of muscle cell membrane showing position of dystrophin

- Becker Muscular Dystrophy (BMD) is a fundamentally similar disease as DMD. Genetic defect is also at the same locus. But clinically BMD is a milder and more protracted disease.

Clinical findings

- Characteristic clinical features are progressive weakness, intellectual impairment, hypertrophy of the calves, and proliferation of connective tissue in muscle.
- Infant boys are rarely symptomatic at birth or in early infancy. Early gross motor skills are usually achieved at the appropriate ages or may be mildly delayed.
- Onset is in early years. There is delay in motor milestones. Typically, boys lose ability to walk between 8 and 12 years.
- There is difficulty in climbing stairs, and lordosis with waddling gait.

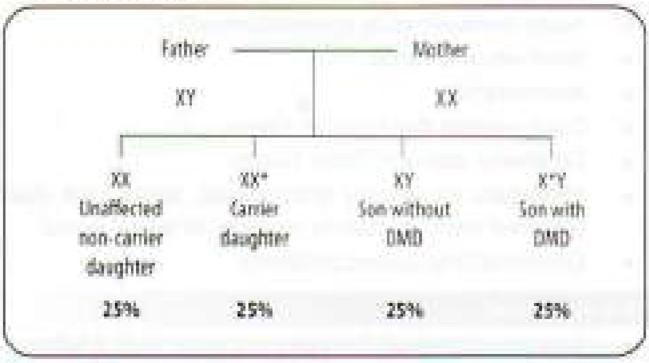


Figure 15.2 : Inheritance of duchenne muscular dystrophy.

- There is pseudo-hypertrophy of calves and progressive muscular weakness. After the calves, the next most common site of muscular hypertrophy is the tongue and muscles of the forearm. Fasciculations of the tongue do not occur.
- The function of distal muscles is usually relatively well preserved, allowing the child to continue to use eating utensils and a pen.
- Contractures most often develop in ankles, knees, hips, and elbows. Scoliosis is also common.
- Respiratory muscle involvement is expressed by a weak and ineffective cough, frequent pulmonary infections, and decreasing respiratory reserve. This leads to respiratory failure.
- Cardiomyopathy is seen in 50–80% of patients with DMD. This may include persistent tachycardia and myocardial failure.
- Mild intellectual impairmentoccurs in all patients. Only 20–30% of patient with DMD have an IQ <70. This is due to the finding that dystrophin deficiency is also expressed in brain.
- Degenerative changes and fibrosis of muscle is a painless process in DMD. There is no myalgias and muscle spasms.
- Death in DMD usually occurs at about 17–20 years of age. Main causes of death are:

  - Respiratory failure
  - Intractable heart failure
  - Pneumonia
  - Aspiration and airway obstruction

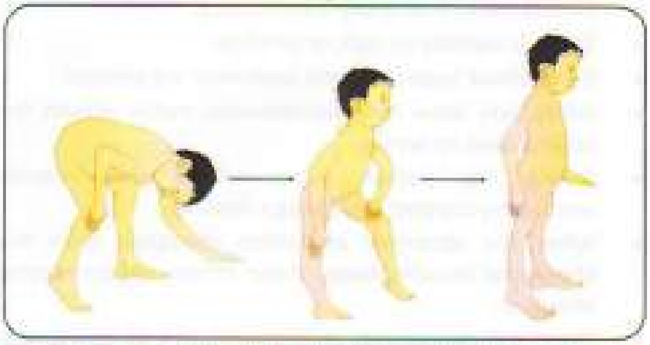


Figure 15.3 : Gower sign in duchenne muscular dystrophy.

Diagnosis

- High plasma Creatine Kinase (CK) level (>15000–35000 IU/L; normal <160 IU/L). This may be high even in presymptomatic stages even at birth. A normal CK level almost excludes the diagnosis of DMD.
- Other less specific lysosomal enzymes present in muscle, such as aldolase and aspartate aminotransferase, are also increased.
- Electromyography (EMG) shows characteristic myopathic features but it is not specific for DMD. There is no evidence of denervation. Nerve conduction (motor and sensory) is normal.

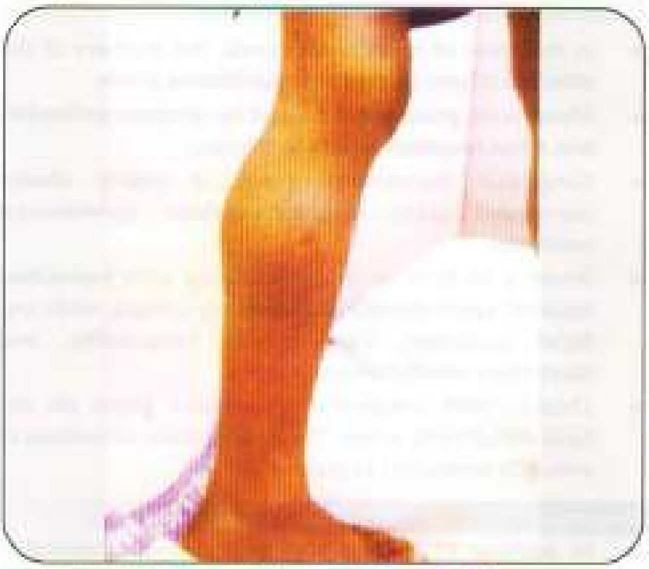


Figure 15.4 : Calf muscle hypertrophy in DMD.

- Polymerase Chain Reaction (PCR) for the dystrophin gene mutation is also a primary test for diagnosis.
- Muscle biopsy is diagnostic and it shows absent dystrophin.
- Cardiac assessment by echocardiography, Electrocardiography (ECG), and radiography of the chest.

Management

- There is no curative medical treatment for Duchenne muscular dystrophy.
- Main treatment is to treat complications and to improve the quality of life.
- Physiotherapy and appropriate seating is needed.
- Steroids have some transient role. Prednisolone (0.75 mg/kg/day) for the first 10 days of each month is given to avoid chronic complications of steroids.
- Cardiac decompensation is treated initially with digoxin.
- Pulmonary infection should be treated promptly.
  - Contact with children having respiratory infections should be avoided.
  - Immunization especially against influenza virus is indicated.
- Nutrition should contain adequate calcium to minimize osteoporosis. Diet should be balanced to prevent obesity.

MYASTHENIA GRAVIS

CASE

A 5-year-old child presents with ***ptosis*** (he has to hold his eyelids open with his fingers) especially in the evening. He also has ***dysphagia*** (trouble swallowing his food). He ***appears sad*** (facial muscle weakness). He is able to run and throw a ball.

- Myasthenia Gravis (MG) is a chronic autoimmune disease causing neuromuscular blockade.
- It is characterized clinically by rapid fatigability of striated muscle, particularly extraocular and palpebral muscles and those of swallowing.
- Myasthenia Gravis occurs in all races, both genders, and at any age. Girls are affected more frequently than boys.
- Myasthenia Gravis occasionally occurs in more than one member of the same family (familialmyasthenia gravis).

Pathophysiology

- The voluntary muscles of the entire body are controlled by nerve impulses that arise in the brain. These nerve impulses travel down the nerves to the place where the nerves meet the muscle fibers. Nerve fibers do not actually connect with muscle fibers. There is a space between the nerve ending and muscle fiber; this space is called the neuromuscular junction.
- When the nerve impulse originating in the brain arrives at the nerve ending, it releases a chemical called acetylcholine. Acetylcholine travels across the space to the muscle fiber side of the neuromuscular junction where it attaches to many receptor sites.

- The muscle contracts when enough of the receptor sites have been activated by the acetylcholine.
- In myasthenia gravis, there is as much as an 80% reduction in the number of these receptor sites. The reduction in the number of receptor sites is caused by an antibody that destroys or blocks the receptor site.
- Antibodies are proteins that play an important role in the immune system. They are normally directed at foreign proteins called antigens that attack the body. Such foreign proteins include bacteria and viruses. Antibodies help the body to protect itself from these foreign proteins.
- For reasons not well understood, the immune system of the person with myasthenia gravis makes antibodies against the receptor sites of the neuromuscular junction. Abnormal antibodies can be measured in the blood of many people with myasthenia gravis. The antibodies destroy the receptor sites more rapidly than the body can replace them.
- Muscle weakness occurs when acetylcholine cannot activate enough receptor sites at the neuromuscular junction.

Clinical findings

- Common symptoms can include:
    - A drooping eyelid. Ptosis increases progressively as patients are asked to sustain an upward gaze for 30–90 seconds.
    - Blurred or double vision
    - Slurred speech
    - Holding the head up from the surface of the examining table while lying supine is very difficult, and gravity cannot be overcome for more than a few seconds. Rapid fatigue of muscles is a characteristic feature of myasthenia gravis.
    - Difficulty in chewing and swallowing
    - Weakness in the arms and legs
    - Chronic muscle fatigue
    - Difficulty in breathing
- Left untreated, myasthenia gravis is usually progressive and can become life-threatening because of respiratory muscle involvement and the risk of aspiration.
- Myasthenic crisis:
    - It is an acute or subacute severe increase in weakness in patients with myasthenia gravis.
    - It is usually precipitated by an intercurrent infection, surgery, or any emotional stress.
    - It may require intravenous cholinesterase inhibitors, immunoglobulin, plasma exchange, gavage feeding, and even transitory ventilator support.
    - Differential diagnosis includes Guillain-Barre syndrome and bulbar poliomyelitis.

Neonatal (transient) myasthenia gravis (infants born to myasthenic mothers)

- Occurs in 12–19% of infants born to myasthenic mothers.
- Infants have respiratory insufficiency.
- There is inability to suck or swallow.
- Generalized hypotonia and weakness are present.
- Infant may show little spontaneous motor activity for several days to weeks.
- During this period, some infants may require ventilatory support and gavage feeding.
- When the abnormal antibodies disappear from the blood and muscle tissue, these infants regain normal strength.
- These infants are not at increased risk of developing myasthenia gravis in later childhood.
- AChR (acetylcholine receptor) antibodies can usually be demonstrated in maternal blood, but at times maternal antibodies may not be detected.

Congenital (persistent) myasthenia gravis

CASE

A newborn presents ***at birth*** with ***severe hypotonia***. Respiratory arrest requires mechanical ventilation. There are no tongue fasciculation. There is history of decreased fetal movements during pregnancy. Plasma Creatine Kinase (CK) is also normal.

- In this form of myasthenia gravis, the mothers of the affected infants rarely have myasthenia gravis.
- Myasthenia gravis is not caused by receptor antibodies and often responds poorly to therapy.
- Congenital myasthenia gravis is nearly always permanent static disorder without spontaneous remission.
- Onset is at birth or in early infancy with hypotonia, external ophthalmoplegia, ptosis, dysphagia, weak cry, facial weakness, easy muscle fatiguability, and respiratory insufficiency or failure.
- Children with congenital myasthenia gravis do not have myasthenic crises. They rarely have elevations of anti-ACh antibodies in plasma.

Diagnosis

- In addition to a complete medical and neurological evaluation, a number of tests may be used to establish a diagnosis of myasthenia gravis.
- **Anti-AChR (acetylcholine receptor) antibody:** A blood test for the abnormal antibodies can be performed to see if they are present. Approximately 85% of myasthenia gravis patients have this antibody and, when detected, is a guaranteed diagnosis.
- **Anti-MuSK (muscle-specific receptor tyrosine kinase) antibody testing:** A blood test for the remaining 15% of seronegative myasthenia gravis patients, those who

have tested negative for the acetylcholine antibody, 40–70% test positive for the anti-MuSK antibody. The remaining patients have an unidentified antibody causing their myasthenia gravis.

- **Neostigmine test:** In newborns and very young infants, the neostigmine test may be preferable to the edrophonium (Tensilon) test.
- **Tensilon test:** The edrophonium chloride (Tensilon test) is performed in older children. This is a clinical test for myasthenia gravis. After administration of a shortacting cholinesterase inhibitor, usually edrophonium chloride, ptosis and ophthalmoplegia improve within a few seconds, and fatigability of other muscles decreases.
- **Electromyography (EMG):** Studies can provide support for the diagnosis of myasthenia gravis when characteristic patterns are present. Electromyography (EMG) is more specifically diagnostic than a muscle biopsy. Repetitive stimulation of a motor nerve at slow rates (3/s) with recording over the appropriate muscle shows a progressive fall in amplitude of the muscle potential in myasthenia gravis.
- The serum creatine kinase level is normal in myasthenia gravis.
- The heart is not involved in myasthenia gravis, and electrocardiographic findings are normal.
- Radiographs of the chest often reveal an enlarged thymus.

Management

- There is no known cure for myasthenia gravis, but there are effective treatments that allow many, but not all, people with myasthenia gravis to lead healthy lives.
- Common treatments include medications, thymectomy and plasmapheresis.
- Spontaneous improvement and even remission may occur without specific therapy.

Medications are most frequently used in treatment.

- Anticholinesterase agents allow acetylcholine to remain at the neuromuscular junction longer than usual so that more receptor sites can be activated.
    - Pyridostigmine bromide: dose is adjusted for each patient. A starting oral dosage is 1 mg/kg per dose every 6 hours.
    - Neostigmine: 15 mg of neostigmine is roughly equivalent to 60 mg of pyridostigmine bromide. Neostigmine causes gastric hypermotility with diarrhea. It is the drug of choice in newborns. It may be given parenterally.
    - Atropine may be added on a maintenance basis to control mild cholinergic side effects such as hypersecretion, abdominal cramps, and nausea and vomiting.
- Corticosteroids (e.g. prednisone), mycophenolatemofetil and immune-suppressant agents (e.g. azathioprine) may be used to suppress the abnormal action of the immune system that occurs in myasthenia gravis.
- Intravenous Immunoglobulins (IVIG) are sometimes used to affect the function or production of the abnormal antibodies also.
- **Thymectomy** (surgical removal of the thymus gland) is another treatment used in some patients. The thymus gland lies behind the sternum and is an important part of the immune system. When there is a tumor of the thymus gland (in 10–15% of patients with myasthenia gravis), it is always removed because of the risk of malignancy. Thymectomy frequently lessens the severity of the myasthenia gravis weakness after some months. In some people, the weakness may completely disappear. This is called a remission. The degree to which the thymectomy helps varies with each patient.
- **Plasmapheresis**, or plasma exchange, may be useful in the treatment of myasthenia gravis also. This procedure removes the abnormal antibodies from the plasma of the blood. The improvement in muscle strength may be striking, but is usually short-lived, since production of the abnormal antibodies continues. When plasmapheresis is used, it may require repeated exchanges.

Treatment of myasthenia gravis crisis

- Sudden difficulties in swallowing and respiration may be observed in myasthenia gravis crisis. Edrophonium results in dramatic but brief improvement.
- Suctioning, tracheostomy, respiratory assistance, and fluid and electrolyte maintenance are required.

Treatment of cholinergic crisis

- Cholinergic crisis may result from overdosage of anticholinesterase drugs.
- The patient may require atropine and tracheostomy.

Complications

- Children with myasthenia gravis do not tolerate neuromuscular blocking drugs (succinylcholine and pancuronium), and may be paralyzed for weeks after a single dose during anesthesia.
- Certain antibiotics (aminoglycosides) can aggravate myasthenia gravis and should be avoided.

Prognosis

- The current treatments for myasthenia gravis are sufficiently effective that the outlook for most patients is bright.
- Although the treatments will not cure myasthenia gravis, most patients will have significant improvement in their muscle weakness.
- In some cases, myasthenia gravis may go into remission for a time, during which no treatment is necessary.

FLOPPY INFANT

CASE

A 3-day old baby presents with very ***poor tone*** and ***floppiness***. He is feeding rather very slowly. There are no other symptoms. On examination, ***limbs not move spontaneously*** (paucity of movement).

- Hypotonia in infancy may be due to a paralytic or a non-paralytic disorder.
- **Paralytic conditions** cause hypotonia with weakness and may affect the anterior horn cells, nerve fibers, neuromuscular junctions or muscles. There is significant lack of movement against gravity or in response to stimuli such as slight pain or tickling.
- **Non-paralytic conditions** cause hypotonia (floppiness) without significant weakness (paralysis).
- The commonest cause of floppy baby is perinatal asphyxia.
- Paralytic causes are mostly genetically determined. Most common paralytic cause of floppy infant is Spinal Muscular Atrophy (SMA).

Causes

Paralytic causes

- Spinal cord disorders: Trauma (e.g. birth injury), tumors
- Anterior horn cell disease: Spinal muscular atrophy, poliomyelitis
- Neuromuscular disorder: Neonatal or congenital myasthenia gravis
- Peripheral neuropathy (very rare)
- Congenital myopathy: Structural (muscular dystrophy) or metabolic (glycogen and lipid storage disorders)

Non-paralytic causes

- Disorders affecting the CNS (birth asphyxia, hypotonic cerebral palsy, Down's syndrome)
- Connective tissue disorders (e.g. Ehlers-Danlos syndrome)
- Prader-Willi syndrome
- Metabolic and endocrine disorders, e.g. hypercalcemia, hypothyroidism
- Benign congenital hypotonia

Clinical findings

- Severely hypotonic infants lie in the characteristic frog-like position.
- On ventral suspension the four limbs hang down and the infant is unable to hold his head up.
- The head lags on pulling to the sitting position.
- There may be deformity of the chest and a "see-saw" respiratory pattern.
- Infants with cerebral palsy may go through a hypotonic phase before becoming spastic.
- Hypotonia at birth is usually due to severe hypoxia, but is occasionally due to drugs taken by the mother e.g. diazepam.
- Benign congenital hypotonia is an idiopathic, non-progressive condition, which tends to improve with age, and is a diagnosis of exclusion.

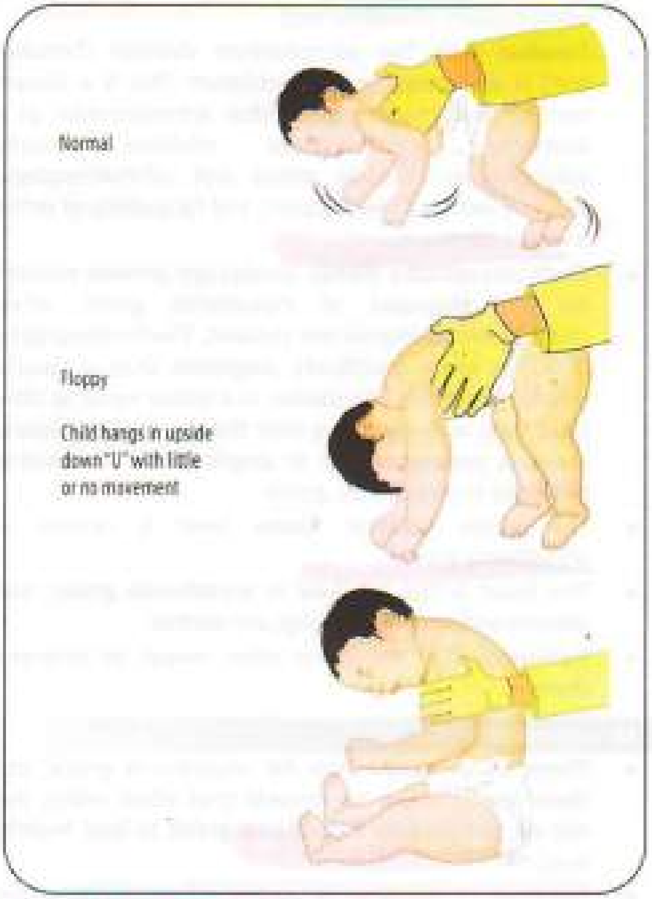

Normal
Floppy
Child hangs in upside down "U" with little or no movement

Figure 15.5 : Normal and floppy infant.

Diagnosis

- Complete urine examination for metabolic errors.
- Serum enzymes: Several lysosomal enzymes (e.g. creatine kinase) are released by damaged or degenerating muscle fibers. The Creatine Kinase (CK) level is characteristically elevated in certain diseases, such as Duchenne muscular dystrophy.
- Thyroid function test
- Serum calcium
- Karyotyping
- Investigations for inborn errors of metabolism.
- CT or MRI scans. There may be evidence of hypoxic damage, e.g. atrophy, cysts.
- Molecular genetic markers: Many DNA markers of hereditary myopathies, including the muscular dystrophies, and neuropathies are available from leukocytes in blood samples.
- Nerve conduction velocity: Neuropathies of various types are detected by decreased conduction.

- Electromyography (EMG) patterns distinguish denervation from myopathic involvement.
- Muscle biopsy:The muscle biopsy is a most important and specific diagnostic study of most neuromuscular disorders. It can detect neurogenic and myopathic processes. It can also detect the type of myopathy and specific enzymatic deficiencies.
- Nerve biopsy is sometimes needed.

SPINAL MUSCULAR ATROPHY (SMA)

CASE

An 8-week-old neonate presents with ***poor feeding*** and floppiness (***hypotonia***). Mother says that baby is not moving his legs since birth. Baby never kicked during pregnancy. On clinical examination, there is ***fasciculations of the tongue*** and ***areflexia***. Electromyography shows evidence of anterior horn cell loss.

- Spinal Muscular Atrophies (SMA) are degenerative diseases of motor neurons.
- SMA begins in fetal life and is progressive in infancy and childhood.
- Upper motor neurons remain normal.
- The heart is not involved in SMA.
- Intelligence is normal.
- There are three main types of SMA, which are due to progressive apoptosis of anterior horn cells.
- The gene is located on chromosome 5.

Type I (Werdnig-Hoffmann disease)

- It is a severe infantile form.
- It is an autosomal recessive condition with a prevalence of 1 in 20,000 births.
- It is rapidly progressive, with the majority dying of respiratory failure within 18 months.
- It presents in the first few weeks of life with weakness and wasting of the muscles.
- Fasciculations are seen, particularly in the tongue.
- There may have been decreased fetal movements and the infant may be profoundly floppy at birth.
- Facial and bulbar muscles are unaffected, so the infant has an alert expression and is able to swallow normally.

Type II

- It is also autosomal recessive disorder.
- It is a more chronic condition, which usually presents between 3 and 12 months of age.
- It causes severe muscle wasting, contractures, and scoliosis.
- Majority of affected children die by the age of 10 years.

Type III (Juvenile) SMA

- It is also called Kugelberg-Welander disease.
- Children develop normally until about 2 years of age, when they develop limb girdle weakness, a waddling gait, and gradual loss of ability to walk.
- Progression of weakness is episodic and usually there is survival into adult life.

Table 15.1: Cardinal features of Werdnig-Hoffmann disease.

Cardinal features of Werdnig-Hoffmann disease
• Severe hypotonia
• Generalized weakness
• Thin muscle mass
• Absent tendon stretch reflexes
• Involvement of the tongue, face, and jaw muscles
• Sparing of extraocular muscles and sphincters

Diagnosis

- Serum Creatine Kinase (CK) level may be normal or mildly elevated.
- Motor neuron conduction studies are normal (an important features distinguishing SMA from peripheral neuropathy).
- EMG shows fibrillation potentials.
- Muscle biopsy reveals a characteristic pattern of perinatal denervation that is unlike that of mature muscle.
- The molecular genetic test of the SMN gene provides definite confirmation of the diagnosis.

Management

- No medical treatment is available to delay the progression of the disease.
- Supportive therapy:
    - Orthopedic care for scoliosis and joint contractures.
    - Mild physiotherapy.
    - Mechanical aids to help the child to eat and to be as functional as possible.

DEGENERATIVE DISORDERS OF CNS

- Characteristic features of a neurodegenerative disease are:
    - Regression and progressive deterioration of neurologic functions
    - Loss of speech, vision, hearing, or locomotion
    - Often associated with seizures, feeding difficulties, and impairment of intellect
- Upper motor neuron signs and progressive spasticity are the characteristics of white matter disorders.
- Convulsions and intellectual and visual impairments are the characteristics of gray matter disorders.

SPHINGOLIPIDOSES

- Sphingolipidoses is a disorder which is characterized by intracellular storage of lipid substrates resulting from defective catabolism of the sphingolipids (which make cellular membranes).
- The sphingolipidoses are sub-classified into:
  - Niemann-Pick disease
  - Gaucher disease
  - GM1 gangliosidosis
  - GM2 gangliosidosis
  - Krabbe disease
  - Metachromatic leukodystrophy

Niemann-Pick disease

- Niemann-Pick Disease (NPD) is a lipid storage disorder that results from the deficiency of a lysosomal enzyme, acid sphingomyelinase.

Clinical findings

- There is a normal appearance at birth.
- Feeding difficulties are common.
- The first symptom detected is usually the presence of hepatosplenomegaly, which is evident at age 3 months and becomes progressively massive.
- Infants fail to thrive.
- Cherry-red spots (cherry-red macula) on ophthalmologic examination. It is due to the deposition of gangliosides in the surrounding retinal ganglion cells.
- Lung infiltrates
- Deafness or blindness
- The disease course is characterized by developmental delay followed by regression.
- Spasticity (initially there is loss of motor function and the deterioration of intellectual capabilities leading to in later stages, spasticity and rigidity).
- Death occurs within 3 years.

Diagnosis

- CBC: Pancytopenia may be present secondary to the enlarged spleen in patients with Niemann-Pick Disease (NPD).
- Chest radiography reveals a typical reticulonodular pattern of infiltration, even in patients with no overt pulmonary symptoms.
- Bone marrow aspirate for *Neimann-Pick cells* (lipid-laden foam cells). Bone marrow examination is not necessary for the diagnosis of NPD.
- White cell enzymes.
  - Measuring the acid sphingomyelinase activity level in peripheral leukocytes, cultured fibroblasts, or lymphoblasts, or a combination of these cells.
- Prenatal diagnosis (can be made reliably by the measurement of acid sphingomyelinase activity in cultured amniocytes or chorionic villi).

Differential diagnosis

- GM1 gangliosidosis
- Gaucher disease

Management

- Currently, there is no specific treatment for Niemann-Pick disease.
- Mainly treatment is supportive.
- Transfusion of blood products may be necessary for acute episodes of bleeding secondary to hypersplenism and thrombocytopenia in NPD patients.

Prognosis

- Niemann-Pick Disease (NPD) disease is fatal in early childhood.

Gaucher disease

CASE

A 10-year-old healthy girl presents with pallor. On physical examination, there is an ***enlarged spleen***. Blood count show ***anemia***, ***leukopenia***, and ***thrombocytopenia***. X-ray of the femur shows an Erlenmeyer flask appearance. ***Bone marrow examination*** shows abnormal cells ***(Gaucher cells)***.

- This disease is a multisystemiclipidosis characterized by:
  - Hematologic problems.
  - Organomegaly
  - Skeletal involvement (bone pain and pathologic fractures)
- It is the most common lysosomal storage disease (autosomal recessive).
- Gaucher disease results from the deficient activity of the lysosomal hydrolase, acid β glucosidase.
- The enzymatic defect results in the accumulation of undegraded glycolipid substrates, particularly glucosylceramide, in cells of the reticuloendothelial system.
- This progressive deposition results in infiltration of the bone marrow, progressive hepatosplenomegaly, and skeletal complications.
- The pathologic hallmark of Gaucher disease is the *Gaucher cell* in the reticuloendothelial system (particularly in the bone marrow).

Clinical findings

- Anemia
- Bleeding tendency (thrombocytopenia)
- Skeletal pain
- Deformities
- Osteopenia
- Splenomegaly is massive than hepatomegaly
- Neurologic manifestations are in type 2

Diagnosis

- Elevated Angiotensin-Converting Enzyme (ACE) and acid phosphatase are markers for the disease.
- Bone marrow aspiration may reveal Gaucher cells.
- Leukocytes or cultured fibroblasts enzymes (acid β glucosidase activity) for glucocerebrosidase give the definitive diagnosis.
- The identification of carriers can be achieved by enzymatic assay. Testing should be offered to all family members.
- Prenatal diagnosis is available by determination of enzyme activity in chorionic villi or cultured amniotic fluid cells.

Management

- Enzyme replacement therapy with recombinant acid β-glucosidase.
  - Most extraskeletal symptoms (organomegaly, hematologic indices) are reversed by an initial dose of enzyme (60 IU/kg) administered by intravenous infusion every other week.
  - Monthly maintenance enzyme replacement improves bone structure, decreases bone pain, and improves growth in affected children.
  - Enzyme replacement does not alter the neurologic progression of patients with Gaucher disease types 2.
- Bone marrow transplant is curative but results in significant morbidity and mortality.
- Splenectomy (corrects thrombocytopenia, anemia, and mechanical problems).
- Gene therapy.
- No effective treatment for type 2 (severe CNS involvement).

GM1 gangliosidoses

CASE

An infant had a normal neurologic examination at birth. Within few months he developed severe progressive ***central nervous system degeneration.*** There is also ***hepatosplenomegaly***, macroglossia, coarse facial features, and a ***cherry-red spot in the eye***.

- It is inherited as an autosomal recessive trait.
- There is a marked deficiency of acid β galactosidase. This enzyme is assessed in leukocytes and cultured fibroblasts. It is also measured in cultured amniotic cells for prenatal diagnosis.
- **Cherry-red spot** is a characteristic finding. It is an opaque ring (sphingolipid-laden retinal ganglion cells) encircling the normal red fovea.

GM2 gangliosidoses

- The GM2 gangliosidoses are autosomal recessive inherited disorders.
- Main subtypes are:
  - Tay-Sachs Disease (TSD)
  - Sandhoff disease.
  - Juvenile GM2 gangliosidosis
  - Adult GM2 gangliosidosis

Tay-Sachs disease (TSD)

- Infants with TSD appear normal until about 6 months of age.
- There may be a marked startle reaction to noise that is present soon after birth.
- By the age of one year, affected children begin to lag in developmental milestones.
- They lose the ability to stand, sit, and vocalize.
- Early hypotonia develops into progressive spasticity.
- Children develop convulsions, blindness, deafness, and cherry-red spots.
- Macrocephaly is due to deposition of GM2 ganglioside in the brain.
- There is a deficiency of the isoenzymehexosaminidase A.
- Diagnosis is by detection in serum or leukocytes of hexosaminidase A. It is also diagnosed by chorionic villus sampling in the first trimester of at risk pregnancy (heterozygote parents).
- Children usually die by 3–4 years of age.

CASE

Tay Sachs disease: A 2-year-old child presents with hypotonia. There is also history of irritability and crying when hearing loud noises.

Sandhoff disease

- Clinical findings are similar to TSD.
- There is progressive loss of motor and language milestones beginning at 6 months of age.
- Seizures, cherry-red spots, macrocephaly, and doll-like facies are present.
- Children with Sandhoff disease may also have splenomegaly.
- Sandhoff disease is diagnosed by finding deficient levels of hexosaminidases A and B in serum and leukocytes.
- Children usually die by 3–4 years of age.

Krabbe disease (globoid cell leukodystrophy)

- Krabbe Disease (KD) is an autosomal recessive neurodegenerative disorder.
- There is severe myelin loss (myelin destruction rather than abnormal myelin formation) and the presence of globoid bodies in the white matter.
- The disease results from a marked deficiency of the lysosomal enzyme galactocerebroside β galactosidase.

- Prenatal diagnosis is possible by the assay of galactocerebroside β-galactosidase activity in chorionic villi or in cultured amniotic fluid cells.
- The symptoms of Krabbe disease appear in the first few months of life. These include excessive irritability and crying, episodes of hyperpyrexia, vomiting, and difficulty feeding.
- Generalized seizures may appear early. As the disease progresses, alterations in body tone with rigidity and opisthotonos appear. Visual inattentiveness as a result of optic atrophy becomes apparent.
- In the advanced stages of the illness, children develop blindness, deafness, absent deep-tendon reflexes, and decerebrate rigidity.
- Most children with Krabbe disease die by 2 years of age.
- MRI and magnetic resonance spectroscopy are used to evaluate the extent of demyelination.
- Umbilical cord blood (stem cell) transplantation is the treatment of choice in asymptomatic babies (without neurologic symptoms).

Metachromatic leukodystrophy

- This is a disorder of myelin metabolism.
- It is inherited as an autosomal recessive trait.
- Metachromatic leukodystrophy is characterized by a deficiency of arylsulfatase A.
- This leads to the accumulation of cerebrosidesulfate within the myelin sheath of the Central Nervous System (CNS) and peripheral nervous system.
- Prenatal diagnosis of Metachromatic Leukodystrophy (MLD) is possible by assaying of arylsulfataseA activity in chorionic villi or cultured amniotic fluid cells.

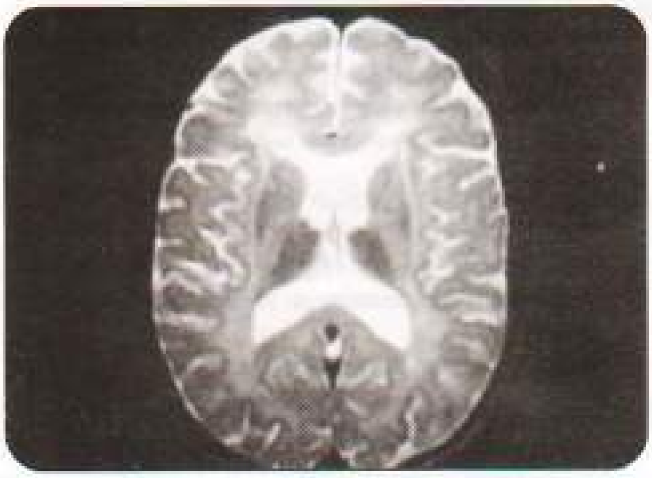


Figure 15.6: CT scan brain: Metachromatic leukodystrophy.

- Metachromatic leukodystrophy begins with insidious onset of gait disturbances between 1 and 2 years of age. The child initially has frequently falls, but gait is gradually impaired significantly and support is required to walk.
- Child is hypotonic, and the deep-tendon reflexes are absent or diminished.
- Within few months, the child can no longer stand. Child is unable to sit unsupported, and progressive decorticate postures develop.
- There is deterioration in intellectual function.
- Speech is slurred and dysarthric. Visual fixation is diminished. Nystagmus is present. Examination of the retina shows optic atrophy.
- There is pseudobulbar palsy causing feeding and swallowing impairment. There are chances of aspiration or bronchopneumonia.
- Neurophysiologic evaluation shows slowing of peripheral nerve conduction velocities. There is progressive change in the auditory brainstem responses.
- CT and MRI images of the brain show diffuse symmetric attenuation of the cerebellar and cerebral white matter.
- Examination of the cerebrospinal fluid shows an elevated protein content.
- Bone marrow transplantation is the only treatment.
- Enzyme replacement therapy is under trial.

ADRENO-LEUKODYSTROPHY (X-LINKED ALD)

CASE

Regression and behavior problems at school: A 7-year-old boy presented with several weeks history of ***lost skills*** and he became clumsy (*ataxia*) and dysarthric. There were ***no dysmorphic features***. On examination, deep tendon reflexes were absent. Very Long Chain Fatty Acid (***VLCFA***) analysis was abnormal (***raised***).

- ALD is a genetically determined disorder.
- It is associated with:
    - Accumulation of saturated Very Low Chain Fatty Acids (VLCFAs).
    - A progressive dysfunction of the adrenal cortex and central and peripheral nervous system white matter.
- This accumulation of fatty acids is caused by genetically deficient peroxisomal degradation of fatty acid.
- The minimum incidence of adrenoleukodystrophy in males is 1 in 21,000.
- Combined incidence of adrenoleukodystrophy in males and heterozygous females in the general population is estimated to be 1 in 17,000.
- All races are affected.

Pathology

- Characteristic lamellar cytoplasmic inclusions (consist of cholesterol esterified with VLCFA) can be demonstrated in adrenocortical cells, testicular Leydig cells, and nervous system macrophages.

- The adrenal dysfunction is caused by a direct accumulation of VLCFAs in cells in the zona fasciculate.

Clinical findings

- Development is usually normal in the first 3–4 years of life.
- Most common initial manifestations are hyperactivity and worsening school performance in a previously well child.
- Auditory discrimination is impaired.
- Tone perception is preserved.
- Spatial orientation is usually impaired.
- There are also disturbances of vision, ataxia, poor handwriting, seizures, and strabismus. This may progress rapidly to increased spasticity and paralysis, visual and hearing loss, and loss of ability to speak or swallow.
- Impaired cortisol response to ACTH stimulation is present in about 85% of children. There is hyperpigmentation.
- Patients may continue in this state for 10 years or more.

Diagnosis

- High levels of VLCFA in plasma, red blood cells, or cultured skin fibroblasts. This is the most specific and important laboratory test.
- Positive results are obtained in:
    - All male patients with ALD.
    - Approximately 85% of female carriers of ALD.
- MRI brain shows:
    - Cerebral white matter lesions that are characteristic of ALD.
    - In 80% of patients, the lesions are symmetric and involve the periventricular white matter in the posterior parietal and occipital lobes.
    - In 12% of patients, the initial lesions are frontal.
    - Unilateral lesions (producing a mass effect suggestive of a brain tumor) may occur.
- Impaired adrenal function:
    - Elevated levels of ACTH in plasma (in >85% of patients with ALD).
    - A subnormal rise of cortisol levels in plasma following intravenous injection of 250 μg of ACTH.

Differential diagnosis

- Attention-deficit disorders or learning disabilities (rapid progression, signs of dementia, or difficulty in auditory discrimination suggest ALD).
- Other leukodystrophies
- Multiple sclerosis
- Cerebral forms of ALD presenting as increased intracranial pressure and unilateral mass lesions should be differentiated from gliomas.

Complications

- Adrenal insufficiency
- Neurologic problems (contracture, coma, and swallowing disturbances)
- Behavioral disturbances
- Injuries associated with defects of spatial orientation, impaired vision and hearing
- Seizures

Management

- Corticosteroid replacement for adrenal insufficiency or adrenocortical hypofunction.
- Lorenzo's oil therapy reduces cerebral progression. Lorenzo's oil (4 : 1 mixture of glyceryltrioleate and glyceryltrierucate) is under investigation.
- Bone Marrow Transplantation (BMT) is only treatment available if considered early (before developing neurologic disability).
- Hematopoietic stem cell transplant is also considered in early disease stage with mild neurologic involvement.
- Supportive therapy is very important in advanced disease and when no other treatment is available.
- Parents and family support about the patient's progressive behavioral and neurologic disturbances.

Genetic counseling and prevention

- Family screening in all at-risk relatives of symptomatic patients.
- Plasma assay of VLCFAs level is a reliable test for identification of asymptomatic males. Plasma VLCFA assay is recommended in all male patients with Addison Disease (ALD) is present in about 25% of boys with Addison disease).
- Monitoring of brain MRI also permits identification of suspected patients at early stage of ALD. At early stage BMT has the greatest chance of success.
- DNA analysis permits accurate identification of carriers.
- Prenatal diagnosis of affected male fetuses can be done:
    - By measurement of VLCFA levels in cultured amniocytes or chorionic villus cells
    - By mutation analysis

GUILLAIN-BARRE SYNDROME (GBS)

CASE

A 10-year-old boy presented with ***weakness in his lower extremities*** two weeks after a mild upper respiratory infection. Now, within a few days, ***weakness progresses*** to include his trunk. On physical examination, he has the weakness of lower limbs and ***absent tendon reflexes***. Spinal fluid examination (***CSF***) is normal but protein level is raised. There is marked slowing of nerve conduction velocity.

- It is an acquired, autoimmune (postinfectious or idiopathic) poly-neuropathy with symmetrical flaccid motor weakness and minimal sensory involvement, typically associated with raised CSF protein but no cells.
- GBS is the most common cause of Acute Flaccid Paralysis (AFP) in all ages. It is not hereditary.
- Major features of GBS are weakness and areflexia.

Epidemiology

- The estimated annual incidence of GBS is approximately 0.4–1.7 cases per 100,000 population.
- GBS is very rare in children younger than 1 year of age.
- There is an approximately 1.5:1.0 male-to-female ratio.
- Male predominance is more significant in adults.

Pathophysiology

- GBS is an immune mediated disease because it is an acquired disease and responds to immunologic therapy.
- A previous gastrointestinal infection with *Campylobacter jejuni* is associated with a more severe form of GBS.
- There may be both demyelinating and axonal injury. Bacteria share antigenic sites with the axon, the peripheral nerve myelin, or both.
- There are multifocal areas of inflammation and demyelination with cellular infiltration of macrophages and lymphocytes.
- Inflammatory response is more severe at the junction of the dorsal and ventral roots at the site of dural attachment.
- Macrophages penetrate the basement membrane of Schwann cells and damage the myelin lamellae, leaving the axon exposed.
- There is conduction block due to focal demyelination. This is detected on electromegnatic studies.
- Characteristic albuminocytologic dissociation of the CSF is due to breakdown in the blood-brain barrier by intense inflammation at the junction of the dorsal and ventral roots and the transudation of plasma proteins into the CSF.
- Traversing axons may be injured due to intense inflammation causing chromatolysis in these areas with neurophagia of the anterior horn cells.
- Inflammation can involve the peripheral nerves, cranial nerves, dorsal roots, dorsal root ganglia, and the sympathetic chain but inflammation is more severe in the proximal nerve roots of the lumbar and brachial plexuses.

Etiology

- It is an antigen–antibody reaction directed against peripheral nerves following respiratory or gastrointestinal infections.
- Mycoplasma and viral infections like hepatitis B virus, Cytomegalovirus, Epstein-Barr virus, Mumps, Measles, Echo, Coxsackie and Influenza viruses have been incriminated or may occur following vaccinations (oral polio, rabies, influenza, meningococcal).
- The viral infection has run its course by the time weakness appears.
- *Campylobacter jejuni* is the most common cause of a diarrheal illness and implicated as a cause of a more severe form of GBS.
- *Haemophilusinfluenzae* has some association with Miller-Fisher syndrome.

Stages of GBS

GBS has three stages:

1. Progressive phase over several days to several weeks. Majority of complications occur in the first phase (which does not persist beyond 6 weeks).
2. A plateau phase of similar duration
3. Recovery over weeks to months

Clinical findings

- These appear about 2 weeks after the onset of viral infection or febrile illness (a nonspecific gastrointestinal or respiratory infection).
- There is a sudden onset of symmetrical weakness in lower limbs in a child who has been vaccinated (for poliomyelitis) properly. Asymmetry is found in 9% of patients.

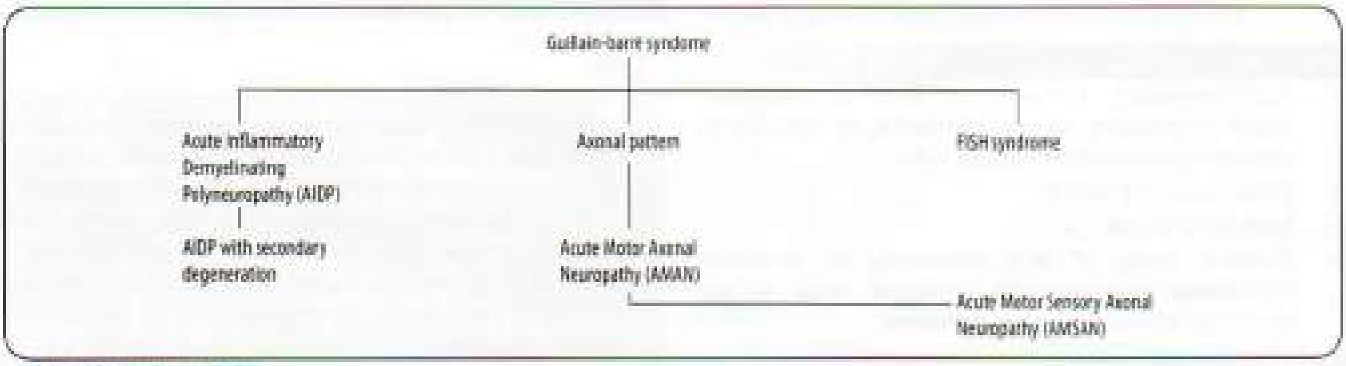

Guillain-barre syndrome
Acute Inflammatory Demyelinating Polyneuropathy (AIDP)
Axonal pattern
FISH syndrome
AIDP with secondary degeneration
Acute Motor Axonal Neuropathy (AMAN)
Acute Motor Sensory Axonal Neuropathy (AMSAN)

Figure 15.7: Variants of GBS

- Muscle weakness spreads in ascending fashion from lower limbs to the trunk, upper limbs and cranial nerves in 3–7 days (Landry ascending paralysis).
- Weakness is associated with hypotonia and hyporeflexia in the lower limbs but plantar responses are normal. 10% may have normal reflexes.
- Early in the course of the disease reflexes may be obtained in the proximal locations but may be absent distally.
- Ascending paralysis with involvement of respiratory muscles and deglutition difficulty is of serious prognosis. About 10–20% of patients progress to respiratory failure requiring mechanical ventilation. Dysphagia and facial weakness are often impending signs of respiratory failure.
- Muscle tenderness and paresthesia in the extremities, around the mouth, or in the back as the presenting symptom may occur but sensory involvement is usually minimal or absent. Pain in a band distribution is common.
- Weakness, sensory loss, and pain, independently or together, often present as a gait disturbance with an ataxic component out of proportion to the muscle weakness.
- GBS should be considered in any child who has an acute gait disturbance.
- Cranial nerves may be involved but facial palsy is most common.
- Signs of meningismus may be present with drowsiness and papilledema and rarely of cerebellar ataxia.
- Fever is not a typical component of the syndrome, and when present, suggests a potential secondary infection.
- Autonomic dysfunction may occur with cardiac arrhythmia, postural hypotension or hypertension. Cardiovascular monitoring is important.
- Sphincter dysfunctions are uncommon but rarely urinary retention may occur.

Miller Fisher syndrome

- A variant of GBS
- Acute onset of ophthalmoplegia
- Ataxia
- Hyporeflexia with elevated CSF protein level
- Subsequent recovery

CASE

Miller Fisher variant of GBS: A 7-year-old boy presents with complaint of seeing double. He has inability to stand steady. On examination, he has inability to gaze upwards and ***right-sided facial weakness***. He also has ***weakness in both legs***. Reflexes are diminished.

Diagnosis

- It is mainly clinical. There is no distinctive test to confirm the diagnosis of GBS
- A diagnosis of GBS is based on

Characteristic clinical features

- History of acute weakness
- Findings of objective muscle weakness and areflexia that have a typical progression compatible with the syndrome

Electrodiagnostic studies

- The most important electrodiagnostic feature in GBS is evidence of multi-focal demyelination in motor and sensory nerves.
- Motor response show a reduction in the Compound Muscle Action Potential (CMAP) as a result of distal demyelination and from loss of axons.
- Conduction block is found less frequently and is asymmetric.
- Nerve conduction velocities are slowed late in the course of the illness.
- Electromyography (EMG) shows a reduction in recruitment, and evidence of active denervation (extensive fibrillations) as a result of axonal destruction.
- Indications for electrodiagnostic studies are:
    - Atypical clinical features
    - A rapidly progressive course
    - Severe or very mild weakness
    - Delayed recovery
    - When diagnosis is confusing

CSF findings

- CSF studies are essential for diagnosis.
- These are characteristic after the first week.
- There is albumino-cytological dissociation (elevated concentration of protein with a normal cell count). CSF protein is elevated to more than twice the upper limit of normal. The proteins are raised between 80–200 mg/dl but cell are around 5–10 cell/mm^3, mainly lymphocytes. There is no pleocytosis. Glucose level is normal.
- A finding of more than 50 cells/mm^3 suggests an alternative diagnosis, as does a neutrophil predominance.

Other relevant investigations

- MRI of the spinal cord may be indicated to rule out disorders of spinal cord (thickening of the caudaequina and intrathecal nerve roots).
- Motor nerve conduction velocities are greatly reduced. Sensory nerve conduction time is usually slow.
- Electromyography (EMG) shows evidence of acute denervation of muscle.
- Serum creatine kinase level may be mildly elevated or normal.

- Antiganglioside antibodies are sometimes elevated.

Table 15.2: Diagnostic features of GBS.

Features required for diagnosis:

- Progressive motor weakness of more than one limb
- Areflexia or marked hyporeflexia

Features strongly supportive of the diagnosis:

- Progression over days to a few weeks
- Relative symmetry
- Mild sensory loss
- Onset with extremity pain or discomfort
- Cranial nerve involvement
- Onset of recovery 2–4 weeks after halt of progression
- Autonomic dysfunction
- Initial absence of fever
- Elevated CSF protein level after one week of symptoms
- Abnormal electrodiagnosis with slowed conduction or prolonged F waves

Features raising doubt on diagnosis:

- Marked, persistent asymmetry of weakness
- Persistent bladder or bowel dysfunction
- Bladder or bowel dysfunction at onset
- Mononuclear leukocytes in CSF >50/mm^3
- Sharp sensory level

Features that rule out diagnosis:

- Evidence of polio, botulism, toxic neuropathy, organophosphates, tick paralysis, hysteria
- Pure sensory syndrome
- History or evidence of lead intoxication
- History or culture evidence of diphtheria
- Evidence of porphyria
- Current history of hexacarbon abuse

Differential diagnosis

Spinal cord lesions

- Acute transverse myelitis
- Epidural abscess
- Tumors
- Poliomyelitis (natural or live virus)
- Enteroviruses
- Vascular malformations
- Cord infarction
- Fibro-cartilaginous embolism
- Cord compression (from vertebral subluxation related to congenital abnormalities or trauma)
- Acute disseminated encephalomyelitis
- Bickerstaff brainstem encephalitis for Miller-Fisher syndrome

Peripheral neuropathies

- Toxic:
  - Vincristine
  - Heavy metal: Gold, arsenic, lead, thallium
  - Organophosphate pesticides
  - Fluoroquinolones
- Infections:
  - HIV
  - Diphtheria
  - Lyme disease
- Inborn errors of metabolism:
  - Leigh disease
  - Porphyria
- Critical illness (polyneuropathy, myopathy)
- Vasculitis syndromes
- Porphyria
- Mitochondrial neurogastrointestinal encephalomyopathy

Neuromuscular junction disorders

- Tick paralysis
- Myasthenia gravis
- Botulism
- Hypercalcemia
- Myopathies
- Periodic paralyses
- Dermatomyositis
- Critical illness (myopathy, polyneuropathy)

Management

General supportive care

- Mainstay of treatment is supportive care
- Patients should be admitted to the hospital for observation. Ascending paralysis can rapidly involve respiratory muscles during the next 24 hours.
- Those whose GBS progresses slowly may require only supportive therapy and monitoring.
- Good medical and nursing care is all, which is required as 80% recover within 2–4 weeks.
- Patients need nutritional support (tube feeding), care of bowel and bladder and frequent change of posture to prevent bedsores (prevention of decubiti in children with flaccid tetraplegia) and prevention of deep vein thrombosis.
- Treatment of secondary bacterial infections is important.

Artificial ventilation

- It is necessary in patients with respiratory paralysis.
- 10–20% of children who have GBS require assisted ventilation.
- A newly diagnosed patient should have forced vital capacity, negative inspiratory force, and vital signs measured every 6 hours at least at the beginning of the illness.

- Indications for assisted ventilation are:
  - Rapidly decreasing vital capacity
  - Breathlessness or signs of fatigue
  - Deterioration of arterial blood gas values
- Dysphagia and/or shoulder weakness is a sign to show that respiratory assistance may be necessary.
- Patients who have cardiovascular instability due to autonomic involvement may also require intubation.
- Tracheostomy is done and patient put on ventilator with frequent suctioning and chest physiotherapy.

Steroids

- Prednisolone 2 mg/kg/day may be given for 2 weeks assuming it to be an allergic disorder.
- Results are not uniformly good.

Plasma exchange

- It is recommended for seriously affected patients within two weeks of illness.
- It removes antibodies but is costly and not risk free.
- The recommended protocol is 250 ml/kg of plasma divided into four to six sessions during the first week of the illness.
- Albumin or fresh frozen plasma both may be used as a replacement volume.

Immunoglobulins

- These have also been tried, with good results.
- It is perhaps the preferred treatment of choice.
- Efficacy is similar to that of plasma exchange.
- Therapy is expensive but simple. Dose is 400 mg/kg/day for 5 consecutive days or 1 gm/kg for 2 consecutive days. Common side effects are nausea and headache.
- Rarely, there is a relapse in a patient treated with IVIG. Such relapses may occur more commonly when IVIG is given early in the course of the disease.
- IVIG is lifesaving in severe cases. Indications for IVIG are in children unable to walk who:
  - Have a very rapidly progressive course
  - Have bulbar paralysis and impending respiratory distress
- Plasmapheresis and/or immunosuppressive drugs are alternatives if IVIG is ineffective.

Prognosis

- The clinical course is usually benign.
- Spontaneous recovery begins within 2–3 weeks.
- Most patients regain full muscular strength. Some patients are left with residual weakness.
- Bulbar function recovers first, and lower extremity weakness resolving last.
- The tendon reflexes are usually the last function to recover.
- The most common causes for death are autonomic disturbances. The second most common cause of death and the most common cause of prolonged hospitalization is respiratory failure.
- Main clinical features predictive of poor outcome with sequelae are:
  - Cranial nerve involvement
  - Intubation
  - Maximum disability at the time of presentation
- The mortality associated with GBS is approximately 3%. Mortality is 10–20% from respiratory insufficiency.
- Almost all of those whom recovery is not complete get normal activities for age, and few are left with severe neurologic deficits (residual muscle weakness and atrophy).
- Children have a better prognosis than adults.

BELL'S PALSY

CASE

A 9-year-old girl, two weeks after ***a viral upper respiratory infection***, presented with a complaint of several days of ***drooping of the left side of her mouth***. She was ***unable to completely shut her left eye***. Her ***smile*** was ***asymmetric***, but her examination is otherwise normal.

- Bell's palsy is an acute unilateral facial nerve palsy that is not associated with other cranial neuropathies or brainstem dysfunction. If a specific reason cannot be found for the weakness, the condition is called Bell's palsy.
- The preceding infectious causes are Epstein-Barr virus, lyme disease, herpes simplex virus, and mumps virus.
- It is a postinfectious allergic or immune demyelinating facial neuritis.
- Sometimes, it is associated with hypertension.

Etiology

- Idiopathic
- Herpes simplex virus type 1
- Varicella-zoster virus
- Otitis media, cholesteatoma
- Mumps
- Trauma
- Schwannoma of facial nerve
- Infiltrative tumor
- Aneurysm or vascular malformation
- Anomalous narrowing of facial canal
- Hypertension
- Guillain-Barré syndrome

Clinical findings

- The main symptom of Bell's palsy is a sudden weakness or paralysis on one side of face that causes it to droop. This may make it hard for the patient to close eye on that side of face.

- Other symptoms include:
    - Drooling
    - Eye problems, such as excessive tearing or a dry eye
    - Loss of ability to taste (anterior two thirds of the tongue)
    - Pain in or behind the ear
    - Numbness in the affected side of face
    - Increased sensitivity to sound
    - Numbness and paresthesias do not occur

Diagnosis

- Physical and neurological examination is needed to check facial nerve function and rule out more serious causes of facial paralysis.
- MRI visualizes the facial nerve within its canal. It shows any bony anomalies, compressive aneurysms, vascular malformations, or nerve sheath or infiltrative tumors. Two sides (both facial nerves) can be compared. Labyrinthine segment within the petrous bone (which is the narrowest site in the facial nerve canal) can be examined.
- Diffusion tensor tractography shows a tridimensional display of facial nerve axons.

Management

- Most patients who have Bell's palsy recover on their own within a few weeks to a couple of months. However, a small number of people may have permanent weakness of the muscles on the affected side of the face.
- Protection of the cornea with ocular lubricants.
- If Bell's palsy is caused by inflammation from another disease, corticosteroids, such as prednisone, may be given to reduce the inflammation. Oral prednisone (1 mg/kg/day for 1 week, followed by a 1 week taper) started within the first 3–5 days of illness.
- Adding oral acyclovir or valacyclovir to the prednisone therapy is also recommended.
- If a specific causative infection is identified, specific antiviral or antibacterial treatment is given.
- Surgery is needed for facial canal if there is nerve compression or any anatomic lesion.
- Laser therapy is used in some cases.
- Physiotherapy to the facial muscles is also recommended.
- Protection of the cornea with methylcellulose eyedrops or an ocular ointment is especially important during sleeping.

Prognosis

- The prognosis is excellent.
- Recovery is spontaneous in more than 80% of cases and there is no residual weakness.
- 10% have mild facial weakness.
- 5% develop permanent severe facial weakness.

Facial palsy at birth

- Facial palsy at birth is usually caused by a compression on facial nerve from forceps application during delivery.
- This condition recovers spontaneously within a few days or weeks.
- Congenital absence of the depressor angularisoris musclealsocauses facial asymmetry. This is especially apparent when an affected infant cries. This is not a facial nerve lesion. Feeding is not disturbed. This defect is due to symmetric calcified infarcts in the tegmentum of the pons and medulla oblongata during late fetal life.

MYOTONIC MUSCULAR DYSTROPHY

CASE

A 2-year-old child presents with history of deformed elbows, stiff neck and tight tendoachilles. Physical examination shows bradycardia. His elder brother has same problem (unable to walk) and is also taking cardiac treatment.

- Myotonic dystrophy is an autosomal dominant condition.
- It is characterized by muscle weakness and tonic muscle spasms (myotonia means an inability to relax muscles at will).

Clinical findings

- Infant are normal at birth
- Facial appearance
    - An inverted V-shape upper lip
    - Thin cheeks, scalloped, concave temporalis muscles
    - Head may be narrow, palate is high and arched
- There is progressive wasting of distal muscles.
- Thenar and hypothenar eminences are flattened.
- Atrophic dorsal interossei leave deep grooves between the fingers.
- Tongue is thin and atrophic.
- There is difficulty with climbing stairs.
- Gower sign is positive.
- Myotonia is a very slow relaxation of muscle after contraction.
- On a handshake, patient grips your hand but has difficulty releasing the grip.
- Speech articulated poorly
- Smooth muscle involvement of GIT causes constipation and encopresis
- There may be cardiac involvement, hypothyroidism, diabetes mellitus, cataracts, or immunologic difficulties.

Diagnosis

- Evaluation of a patient for myotonic dystrophy includes neurological examination, Electromyography (EMG) assessment and obtaining serum for genetic testing.
- CK (creatine kinase) is elevated.
- ECG
- USG to determine diaphragmatic function
- Thyroid and adrenal cortical function assessment
- Glucose tolerance test
- Immunoglobulin studies
- Genetic testing: DNA analysis of blood. There is a part of chromosome 19 which is expanded in those with myotonic dystrophy.
- The EMG shows a typical myotonic discharge which has a waxing and waning quality.
- Muscle biopsy

Management

- No specific medical treatment is available
- Genetic counseling
- Treatment of cardiac, endocrine, GIT, ocular complications
- Nutrition support in very affected children may require tube feedings
- Physiotherapy
- Orthopedic treatment of contractures
- Drug therapy
    - Phenytoin
    - Carbamazepine
    - Procainamide
    - Quinidine sulfate
- Patients with myotonic dystrophy should be aware of a special vulnerability when undergoing anesthesia.

SYRINGOMYELIA

- Syringomyelia refers to a cystic collection that occurs within the spinal cord around the central canal.
- Term "syrinx" is sometimes used to refer to a fluid collection within the cord.

Types

Communicating syringomyelia

- Cerebrospinal Fluid (CSF) from within the ventricles communicates with the fluid within the spinal cord.
- It is assumed to be the source of the CSF that distends the spinal cord.

Non-communicating syringomyelia

- Ventricular CSF does not communicate with the fluid within the spinal cord.
- It primarily occurs in the presence of intra-medullary tumors and obstructive lesions.

Post-traumatic syringomyelia

- Spinal cord injury results in damage, softening of the spinal cord and scarring of the surrounding spinal cord tissue. This results in progressive distention of the cyst.

Associations

- Chiari anomalies
- Ehlers-Danlos syndrome

Clinical findings

- Signs and symptoms of syringomyelia may be acute or chronic.
- Syringomyelia usually involves the cervical area. Symptomatic presentation depends primarily on the location of the lesion.
- Syrinx interrupts the spinothalamicfibers that mediate pain and temperature sensibility, resulting in loss of these sensations, while light touch, vibration, and position senses are preserved (dissociated sensory loss).
- When the cavity enlarges to involve the posterior columns, position and vibration senses in the feet are lost.
- A syrinx may extend into the medulla, producing a syringobulbia. This syndrome is characterized by:
    - Dysphagia
    - Nystagmus
    - Pharyngeal and palatal weakness
    - Asymmetric weakness and atrophy of the tongue
    - Sensory loss involving primarily pain and temperature senses in the distribution of the trigeminal nerve
- A complete physical examination may reveal diminished arm reflexes, which are sometimes present early in the clinical course of syringomyelia.
- Lower limb spasticity, which may be asymmetrical, appears with other long-tract signs such as paraparesis, hyperreflexia, and extensor plantar responses.
- Classic presentation is called the central cord syndrome.
    - There is numbness beginning in the shoulder, atrophy and weakness in the upper extremities and trophic ulcers of the hands.
    - Central cord syndrome results from damage to the central spinal cord and selective involvement of the upper rather than the lower extremities.
- Other forms of presentation of syringomyelia include:
    - Scoliosis (rapidly progressive, absence of superficial abdominal reflexes)
    - Urgency and bladder dysfunction
    - Lower extremity spasticity
    - Severe pain in the area of the spinal cord distention above the level of the injury
    - An ascending level of motor and sensory dysfunction

Complications

- Complications are due to myelopathy and include:
    - Recurrent pneumonia
    - Paraplegia or quadriplegia
    - Decubitus ulcers
    - Bowel and urinary dysfunction

Diagnosis

- MRI is the radiologic study of choice. It may show:
    - Cranio-vertebral junction (association of syringomyelia is with Chiari I and II malformations).
    - Obstruction to the flow of CSF from the fourth ventricle (can cause syringomyelia).
- Myelography is performed in special situations when MRI cannot be used. Widening of the cord and complete subarachnoid block may be observed.

Management

- No medical treatment is known for patients with syringomyelia.
- The treatment of syringomyelia is based on the treatment of the underlying cause.
- If the cause can be removed, the syrinx improves.
- In cases of complete spinal cord injury, the most effective treatment is the transection of the spinal cord (drain the syrinx and detether the spinal cord).
- Microscopic lysis of the scar surrounding the spinal cord at the point of spinal injury may prevent from being distorted.
- Decompression of the craniovertebral junction is usually effective in the management of the syringomyelia.
- In a case of non-communicating syringomyelia, management should be directed to tumor resection or to decompression of constricting elements.
- Drainage procedures are used temporarily for symptomatic and radiographic improvement.
- Syrinx-to-subarachnoid shunting with a small piece of shunt tubing may be a treatment in selected cases. Other options are syrinx-to-pleural or syrinx-to peritoneal shunting.

Prognosis

- Prognosis depends on the:
    - Underlying cause
    - Magnitude of neurological dysfunction
    - Location and extension of the syrinx
- Patients with central cord syndrome have poor response to treatment.

TRANSVERSE MYELITIS

CASE

A previously well 12-year-old child (***vaccinated*** against poliomyelitis as an infant) develops ***weakness of both lower limbs*** and inability to pass urine. There is no history of trauma. He is conscious and fully oriented. Tone is decreased in both lower limbs. Power is grade 5/5 in both upper limbs but grade 2/5 in lower limbs. Reflexes in the upper limbs are normal, knee jerks are absent bilaterally. Abdominal reflex is absent and urinary bladder is palpable up to umbilicus. He has a ***sensory level*** at the mid-thorax (T_4).

- **Acute Transverse Myelitis (ATM)** is an inflammatory condition.
- It affects both halves of the spinal cord and is associated with rapidly progressive motor, sensory and autonomic dysfunction.
- Classic findings are:
    - Para or tetraparesis
    - Sensory impairment level
    - Sphincter dysfunction

Etiology

- Idiopathic
- Secondary
    - Acute infection (most commonly viral)
    - Post-infection
    - Post-vaccination
    - Autoimmune
    - Systemic malignancy

Clinical findings

- There is abrupt onset of progressive weakness and sensory disturbances in the lower extremities.
- Low back or abdominal pain is present. There may be paresthesia of the legs.
- Leg muscles are weak and flaccid.
- A sensory level is present, usually in the mid-thoracic region.
- Sphincter disturbances
- Flaccidity gradually changes to spasticity

Differential diagnosis

- Meningitis
- Guillain-Barre syndrome
- Poliomyelitis
- Spinal cord neoplasm
- Epidural abscess
- Demyelinating disorders (a vascular malformation)

Diagnosis

- Examination of CSF
    - Moderate lymphocyte pleocytosis
    - A normal or slightly elevated protein level

- MRI: Up to 40% of cases have no findings on MRI. In the remainder, the appearance is variable and non-specific.

Management

- Treatment of secondary ATM depends on the underlying cause.
- No treatment currently available for idiopathic ATM.
- Spontaneous recovery occurs over a period of weeks or months.
- The initial treatment of patients suspected to have spinal cord lesions includes evaluation of airway, breathing, and circulation.
- A history of trauma requires initial immobilization of the spinal cord until imaging studies and neurological evaluations rule out trauma-related myelopathy.
- Attendance to acute urinary retention should be managed with catheterization (bladder care).
- Physiotherapy
- High dose methyl-prednisolone therapy 30 mg/kg/day for 5 to 7 days, with a maximum dose of 1 g/day. Use of high-dose corticosteroids can reduce the length of disability and improve outcomes.
- If clinical improvement does not begin or symptoms are worsening within 24 to 48 hours of beginning corticosteroid treatment, consideration should be given for initiation of plasma exchange therapy.

CHAPTER 16

Hematologic Disorders

- Hematologic disorders are those that produce either quantitative or qualitative defects in the cellular elements of the blood or in those soluble elements related to hemostasis.

Hematopoiesis

- Hematopoietic tissue is derived from the mesenchymal layer of the embryo.
- Earliest evidence of hematopoiesis is seen in the blood islands of the yolk sac at 2–3 weeks of gestation.
- At 5–6 weeks gestation, hematopoiesis starts in the liver. Liver is the chief site of blood cells production until the 6th fetal month. Liver continues to produce hemic cells until 2 weeks after birth.
- Spleen, lymph nodes, and thymus are also sites of hematopoiesis during fetal life.
- Bone marrow is the site for hematopoiesis at 4–5th fetal month. By the 6th month, bone marrow becomes the chief focus of blood cell production.
- The earliest hemoglobins detected are Gower and Portland. They disappear by the third month.
- HbF ($\alpha_2\gamma_2$), the predominant Hb after the 8th gestational weeks, rises to 90% of the total Hb by the 6th month of gestation. HbF gradually declines to 70% by the end of a term gestation and continues to fall postnatally to adult levels (<2%) by 12 months of age.
- HbA ($\alpha_2\beta_2$) is the predominant adult hemoglobin. It appears in small amounts very early in gestation and rises to 30% of the total Hb at term and to 95% by 1 year of age.
- The other adult hemoglobin, HbA$_2$ ($\alpha_2\delta_2$), reaches the normal adult level of 2% to 3.4% by 1 year of age.
- At birth, hematopoiesis is present in most of the bones, especially in the bone marrow of the long bones. With progressive age active marrow gradually reduces from the distal portions of the skeleton.

ANEMIA

Definition

- Anemia is present when there is a decrease in the level of hemoglobin in the blood below the reference level for the age and sex of the individual
- Anemia is defined as a state in which hemoglobin concentration or red cell volume is 2 standard deviation below the mean for that age or sex.
- Anemia is not a disease itself but is a symptom of another disorder.

General considerations

- Alterations in the level of hemoglobin may occur as a result of changes in the plasma volume.
  - A reduction in the plasma volume will lead to spuriously high hemoglobin (e.g. in dehydration).
  - A raised plasma volume produces a spurious anemia (e.g. in congestive cardiac failure). After a major bleed, anemia may not be apparent for several days until the plasma volume returns to normal.
- Patients with anemia may be asymptomatic. Non-specific symptoms due to anemia of any reason are fatigue, headaches, faintness, breathlessness, or palpitations. There is pallor, tachycardia, systolic flow murmur, or cardiac failure.
- Specific signs of different types of anemia may be present e.g. koilonychias in iron deficiency anemia, jaundice in hemolyticanemia, and bone deformities in thalassemia major.

Table 15.1: Normal red blood cell values in the pediatric years.

Age	Mean hemoglobingm/dl	Mean hematocrit (%)
1–3 days (term infant)	18.5	56
1 month	14	43
2–6 months	11.5	35
½-2 years	12	36
2–6 years	12.5	37
6–12 years	13.5	40
12–18 years		
Female	12–14	41
Male	13–14.5	43

- To evaluate a patient with anemia a careful history and examination of the patient is very important.
- A dietary history is important in a case of nutritional anemia.
- Note any family history of anemia or jaundice (thalassemia).

- Note the presence or absence of jaundice (thalassemia, hemolysis, liver disease), irritability or pica (iron deficiency or lead poisoning).
- Jaundice and/or splenomegaly are present in a case of thalassemia.
- There may be delayed growth and development in chronic diseases.
- Note the signs of high-output congestive cardiac failure.
- Epistaxis or easy bruising may be present in leukemia or aplastic anemia.
- In malabsorption syndromes, there is chronic diarrhea.
- In case of hemolyticanemia, note possible precipitating factors such as viral illness or the use of medications.

Classification

Microcytic anemia

- Iron deficiency anemia
- Thalassemia
- Lead poisoning
- Chronic diseases (e.g. infection, cancer, renal disease, inflammation)
- Copper deficiency
- Sideroblastosis

Macrocytic anemia

- Vitamin B_{12} deficiency
- Folate deficiency
- Liver disease
- Hypothyroidism
- Thiamine deficiency
- Vitamin B_6 deficiency (some)
- Myelodysplasia

Normocytic anemia

- Decreased production
    - Aplastic anemia
    - Pure red cell aplasia
    - Leukemia
    - Storage diseases
    - Osteopetrosis
- Blood loss
- Sequestration
- Hemolysis
    - Hemoglobinopathies
    - Hereditary spherocytosis
    - Autoimmune diseases
    - Toxins
    - Infections
    - DIC
    - Hemolytic uremic syndrome
    - Paroxysmal nocturnal hemoglobinuria
    - Hypertension, cardiac disease

CONGENITAL HYPOPLASTIC ANEMIA

DIAMOND-BLACKFAN ANEMIA

CASE

A 3 weeks old infant presents for the evaluation of pallor. He has ***macrocytic anemia***, ***reticulocytopenia*** and microcephaly (***skeletal abnormalities***). Bone marrow shows decreased erythropoiesis.

- Diamond–Blackfananemia is a rare cause of anemia (congenital bone marrow failure syndrome) in infancy.
- This is a pure red blood cell aplasia.
- There is normochromic and macrocytic anemia, reticulocytopenia, and insufficiency or absence of Red Blood Cell (RBC) precursors. Other cell lines are normal in bone marrow examination.
- About 50% of affected infants have extrahematopoietic anomalies.

Clinical findings

- Presents in infancy with pallor, anemia, and congestive heart failure.
- Craniofacial abnormalities are the most common (50% of infants). There is microcephaly, hypertelorism, snub nose, and high arched palate, cleft palate, congenital glaucoma, congenital cataract, strabismus, absent kidneys, or horseshoe kidneys.
- There is short stature, triphalangeal thumb, or flat thenar eminence.
- Radial pulse may be absent.

Diagnosis

- Macrocytic anemia (no hypersegmented neutrophils or other characteristics of megaloblasticanemia).
- Reticulocytopenia
- Normal platelets and white cells
- Increased fetalHemoglobin (Hb)
- Elevated erythrocyte Adenosine Deaminase (ADA): This differentiates congenital hypoplasticanemia from transient erythroblastoma of childhood.
- Fetal antigen present
- Bone marrow shows decreased or absent erythropoiesis.

Differential diagnosis

- Transient erythroblastopenia of childhood (usually presents later)
- Other inherited macrocytic bone marrow failure syndromes, particularly Fanconianemia and Shwachman-Diamond syndrome
- Renal failure with low erythropoietin or erythropoietin antibodies
- Anemia of chronic disease
- Hypothyroidism
- Postinfectious (parvovirus B19 causes red cell aplasia)

- Drug reactions (isoniazid, sulfa drugs, chloramphenicol, azathioprine, antiepileptics)

Management

- Corticosteroids improve bone marrow erythropoiesis in 80% of patients.
- Chronic transfusion therapy for those unresponsive to corticosteroids.
- Spontaneous remission of anemia may occur.
- Hematopoietic stem cell transplantation is curative.

TRANSIENT ERYTHROBLASTOPENIA OF C

CASE

A 2-year-old child presents for evaluation of ***pallor***. He is ***otherwise normal*** without any other physical abnormalities. Dietary history is adequate. There is normocytic anemia with low reticulocyte count.

- Transient Erythroblastopenia of Childhood (TEC) is the most common acquired red cell aplasia in children.
- This is a transient hypoplasticanemia of previously healthy children between 6 months to 3 years of age.

Clinical findings

- Most common presentation is pallor in a relatively well child.

Diagnosis

- Normocytic anemia with low reticulocyte count
- No hemolysis
- No hepatosplenomegaly or lymphadenopathy
- Coombs test negative
- RBC adenosine deaminase levels are normal.
- Bone marrow shows isolated absence of Red Blood Cell (RBC) precursors and rules out other disorders.

Differential diagnosis

- Diamond-Blackfananemia
- Hemolyticanemia in aplastic crisis
- Malignancy (especially acute leukemia)
- Iron, folate, or vitamin B_{12} deficiency
- Anemia of chronic disease—inflammatory bowel disease, autoimmune hepatitis, collagen vascular diseases

Management

- Resolution is usually spontaneous in 4–8 weeks.
- Monitor patient for signs of cardiac decompensation in case of severe anemia.
- Transfusion occasionally needed for anemia causing cardiac decompensation.
- Monitor routine Complete Blood Count (CBC). Recovery is preceded by increase in reticulocyte count.

MICROCYTIC ANEMIA

IRON DEFICIENCY ANEMIA

CASE

A 9-month-old infant presents with ***pallor***. He is ***taking only cow's milk***. He ***eats very little solid food***. Results of physical examination are otherwise normal but he is tachycardiac and pale. Stool is negative for blood. His ***hemoglobin is 8 g/dL*** and hematocrit is 24%.

- Iron deficiency anemia is a disorder characterized by iron deficiency resulting in a microcytic, hypochromic anemia.
- Anemia due to iron deficiency is the most common hematologic disease of infancy and childhood.
- Rapid growth, insufficient dietary intake, and limited absorption of dietary iron combine to place children at increased risk for iron deficiency.
- Iron is necessary for many biologic processes, including oxygen transport. Most iron in the body is found in hemoglobin. Iron is necessary for growth and replacement of daily iron losses is supplied by the diet. Iron is transported in plasma by a specialized transport protein called transferrin. Iron stores are concentrated in the liver, bone marrow, and spleen in the form of ferritin, from which iron can be mobilized readily.
- The body of the newborn infant contains 0.3–0.5 g of iron. Adult iron content is 5 g. To approach adult level, 0.8–1.5 mg of iron must be absorbed each day from the diet. Because less than 10% of dietary iron is absorbed from the diet, 8–15 mg of iron daily is necessary in nutrition.
- Iron deficiency progresses slowly. Initially, iron stores are depleted, although red blood cell production continues. The Red Cell Distribution Width (RDW) is the earliest detectable laboratory change. This is a measure of the variation in size of red blood cells and can be used to detect increased anisocytosis. RDW greater than 14.5% is consistent with iron deficiency.
- As iron stores are depleted further, serum ferritin levels decline. Serum ferritin is an accurate indicator of tissue iron stores. In iron deficiency, serum ferritin levels are less than 8–12 µg/l. As iron deficiency continues, serum iron decreases to less than 30 µg/dl.
- Total Iron Binding Capacity (TIBC) measures the amount of iron that can bind to serum proteins. As iron stores are depleted, TIBC begins to increase.
- Transferrin saturation provides a measure of the iron available for hemoglobin synthesis. Hemoglobin synthesis is impaired at saturations of 10–15%.
- Iron is absorbed more efficiently from human milk than from cow's milk. So, the diets of formula-fed or cow milk-fed infants should include iron fortified cereals or formula to prevent iron deficiency. Newborn infant has iron stores for blood formulation for the first

6–9 months of life; therefore, dietary iron deficiency is uncommon before 9–24 months of age (unless mother anemic).

- Infants with iron deficiency anemia usually have history of consumption of large amounts of cow's milk and carbohydrates un-supplemented with iron. Blood loss also must be considered.
- In addition to causing anemia, iron deficiency has adverse effects on behavior and cognitive function (apathy, irritability, poor concentration). These result from alterations of iron-containing enzymes (monoamine oxidase) and cytochromes.

Etiology

Nutritional

- Mother anemic, repeated pregnancies
- Increased iron demands (preterm, low-birth-weight babies, congenital cyanotic heart disease)
- Prolonged breastfeeding, cow milk
- Poor weaning (no meat or green vegetables)
- Impaired absorption of iron (malabsorption, celiac disease)

Blood loss

In neonates

- Feto-maternal transfusion.
- Twin-to-twin transfusion
- Obstetric complications such as placental abruption or placenta previa
- Bleeding from umbilical cord
- Hemorrhagic disease of newborn
- Cow milk protein allergy

In children

- Hookworm infestation
- Meckel's diverticulum
- Peptic ulcer disease
- Rectal polyps
- Inflammatory bowel disease

Clinical findings

- Mild iron deficiency is relatively asymptomatic.
- As it becomes more severe, the infant manifests:
    - Irritability
    - Anorexia
    - Lethargy
    - Easy fatigability
- Milk-fed infant is fat, pale, and sallow
- Other findings include:
    - Tachycardia
    - Systolic murmur
- If the anemia is very severe (Hb<3 gm/dl), there may be signs of congestive heart failure:
    - Gallop rhythm
    - Cardiomegaly
    - Distended neck veins
    - Hepatomegaly
    - Rales

Diagnosis

- **Hemoglobin level** is low.
- The **reticulocyte** count is normal or minimally elevated.
- **Leukocyte counts** are normal.
- **RBC morphology** shows microcytic hypochromic anemia (erythrocytes become smaller than normal with decreased hemoglobin content). Anisocytosis, poikilocytosis may be seen.
- **Mean Corpuscular Volume** (MCV), **Mean Corpuscular Hemoglobin** (MCH), and **Mean Corpuscular Hemoglobin Concentration** (MCHC), all are reduced.
- **Serum iron level** is decreased.
- **Iron-binding capacity** (the transferrin level) is increased, and the percentage of saturation is low (usually less than 20%).
- **Serum ferritin level** is decreased (which is a reflection of low iron stores in bone marrow).
- **Bone marrow examination** usually is not indicated, but when performed, it shows micro-normoblastic hyperplasia of erythroid elements and decreased or absent stainable iron.

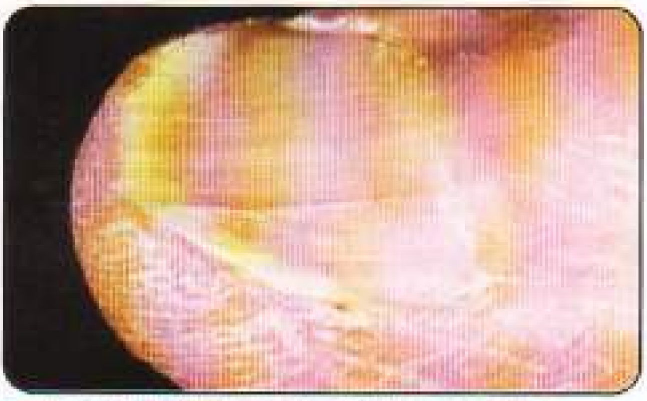


Figure 16.1: Koilonychia in iron deficiency anemia.

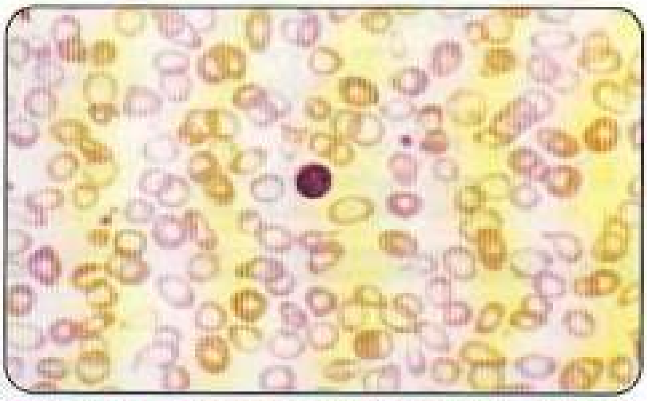


Figure 16.2: Microcytic anemia in iron deficiency. Peripheral blood smear shows small Red Blood Cells (RBCs) that have marked hypochromic central pallor.

Differential diagnosis

- The differential diagnosis of microcytic, hypochromic anemia is:
    - β-thalassemia (normal or increased levels of serum iron and ferritin, normal iron-binding capacity, elevated HbF and HbA_2, hepatosplenomegaly)
    - Lead poisoning
    - Anemia of chronic inflammation or infection

Prevention

- Breastfeeding should be encouraged.
- Addition of supplemental iron is recommended at 4 month of age in breastfed babies.
- Infants who are not breastfed should receive iron-fortified formula for the first year.
- Encourage the ingestion of food richer in iron.

Management

- Goals of therapy are to return the hemoglobin to physiologic levels.
- **Iron therapy:** Mild to moderate anemia without signs of cardiac decompensation can be managed by administration of iron. Oral iron is given at a dosage of 3–6 mg/kg/day of elemental iron. Medicinal iron should be administered between meals to ensure good absorption. After starting iron therapy, there is a rapid subjective improvement in neurologic function within 12–24 hours. Reticulocytes begin to increase within 48–96 hours (peak at 5–7 days). Hemoglobin begins to increase within 4–30 days (rate of hemoglobin rise is about 0.1–0.4 g/dL/day). It takes about 1–3 months for repletion of iron stores. So, treatment is continued for a period of 2–3 months after the hemoglobin level has returned to normal. This allows replenishment of tissue iron stores. Parenteral iron administration is used occasionally when there is diarrhea or poor compliance. Total dose is calculated as:

  mg iron = desired rise in Hb (g/dl) × weight (kg) × 3
- **Dietary Counseling** should also be given. In infants give iron fortified milk formula. At weaning age, give eggs, meat, apple juice, and green vegetables.
- **Blood transfusion:** In severe anemia with signs of cardiac decompensation, packed red blood cells (2–3 ml/kg), are transfused very slowly and repeated in 12–24 hours if necessary.
- Correct any cause of chronic blood loss.
- Correct underlying disorders i.e. malabsorption.

BETA-THALASSEMIA

CASE

A 2-year-old boy presents with pallor and prominent cheeks. Parents are cousins. On clinical examination, he has mild jaundice, growth retardation, and ***hepatosplenomegaly***. Hemoglobin is 5.2 g/dl, MCV 65 fl and **HbF 35%**.

Definition

- It is characterized by the absence or decreased synthesis of the beta globin chain of hemoglobin.

Types of beta-thalassemia

1. Heterozygous states

- Thalassemia Minor:

2. Homozygous states

- Thalassemia Intermedia:
    - 2 beta-thalassemia genes (later-onset)
- Thalassemia Major:
    - 2 beta-thalassemia genes (early onset)

Types of expression

Beta$^+$ (β^+)

- Reduced beta-globin chain synthesis

Beta^0 (β^0)

- Absent beta-globin chain synthesis

Main points

- Inheritance of beta-thalassemia is autosomal recessive.
- Adult hemoglobin constitutes 2 alpha and 2 beta chains [HbA_1 ($\alpha_2 + \beta_2$)].
- Fetalhemoglobin constitutes 2 alpha and 2 gamma chains [HbF ($\alpha_2 + \gamma_2$)].
- The genes controlling beta chain production are located on chromosome 11.

Pathophysiology

Beta-thalassemia minor

- This is the most common form of thalassemia.
- Beta chain production is less than normal due to the failure of one of the genes coding for beta chains.
- Alpha chain production continues at a near normal rate.
- The excess alpha chains and this stimulates the increased production of delta chains. The alpha and delta chains combine to form increased amounts of hemoglobin A_2 [HbA_2 ($\alpha_2+\delta_2$)].

Hereditary Persistent Fetalhemoglobin (HPFH)

- There is decreased production of β and δ-globin chain with increased production of γ-globin chain as compensating element in the form of HbF (20–70%).
- There is only mild anemia and microcytosis and should not be treated with blood transfusions.
- In α-thalassemia, there is absence or reduction in α-globin production.

Beta-thalassemia major

- These patients are well at birth but develop a life-threatening anemia by three or four months.
- In beta thalassemia major there is a complete failure of beta chain production.

- Delta and gamma chains raise levels of hemoglobin A_2 and hemoglobin F.
- Hemoglobin F has a very high affinity for oxygen and is a poor oxygen deliverer. As a result the only functional hemoglobin present is hemoglobinA_2, hence the patient is hypoxic which causes increased erythropoietin secretion. The excess erythropoietin stimulates the marrow to the maximum, and ultimately to the point that extra-medullary hemopoiesis occurs with splenomegaly.
- Even with increased production of hemoglobin A_2 and F, there are still excess alpha chains and they precipitate in the developing normoblasts. This results in intra-medullary hemolysis and their premature removal from the marrow by the reticuloendothelial cells.

Clinical findings

Thalassemia minor

- The growth and development of patients with this disorder are normal.
- The only abnormality is mild anemia (a hemoglobin level that is approximately 10 gm/dl).

Thalassemia intermedia

- In thalassemia intermedia, patients are symptomatic by 2–4 years of age (but CBC may show anemia during the first year of life).
- There is moderate anemia.
- Main complications are hepatosplenomegaly, growth failure, jaundice, and thalassemicfacies.

Thalassemia major

- In thalassemia major (Cooley anemia), patients are symptomatic by 12 months of age (often as early as 3 months).
- There is severe anemia and icteric tinge.
- There is mandibular prominence, depressed nasal bridge, and frontal bossing.
- Abdomen becomes protuberant due to massive hepatosplenomegaly (extramedullaryhematopoiesis).
- Iron overload results in:
    - Hepatic fibrosis and cirrhosis (by age 5 years)
    - Darkening of skin (iron-stimulated melanin production)
    - Sideroblastic cardiomyopathy (arrhythmias, CCF, recurrent pericarditis)
    - Endocrinopathies (e.g. diabetes mellitus, hypothyroidism)
- Others complications are:
    - Recurrent infections
    - Septicemia, failure to thrive
    - Growth retardation

Differential diagnosis

- Other causes of mild microcytic, hypochromic anemias (iron deficiency and α-thalassemia).

Diagnosis

Complete blood count

- In thalassemia major, hemoglobin usually falls 5–6 g/dl or less. Hb is usually normal in thalassemia minor.

Retics

- Relatively increased 5–10%

RBC morphology

- Microcytic hypochromic anemia
- Anisocytosis, poikilocytosis, target cells, nucleated RBCs, precipitated alpha chain inclusions (Heinz bodies).

Hemoglobin electrophoresis

- It is diagnostic.
- Thalassemia Minor:
    - Decreased HbA_1
    - Elevated HbA_2 up to 10% (normal 2.5%)
    - Elevated HbF up to 7% (normal <2.0%).
- Thalassemia Intermedia; $Beta^+$:
    - Decreased HbA_1 (20–40%)
    - HbA_2 always elevated
    - HbF is 60–80% of total hemoglobin
- Thalassemia Major; $Beta^0$:
    - Absent HbA_1
    - Elevated HbA_2 (>3%)
    - T2, MRS for iron overload of liver and heart.

Serum

- Serum iron is elevated.
- Saturation of Total Iron Binding Capacity (TIBC).
- Normal or elevated bilirubin.

Imaging studies

- X-rays in thalassemia major:
    - "Hair–on–end" pattern in the skull
    - Thinning of the long bone cortices

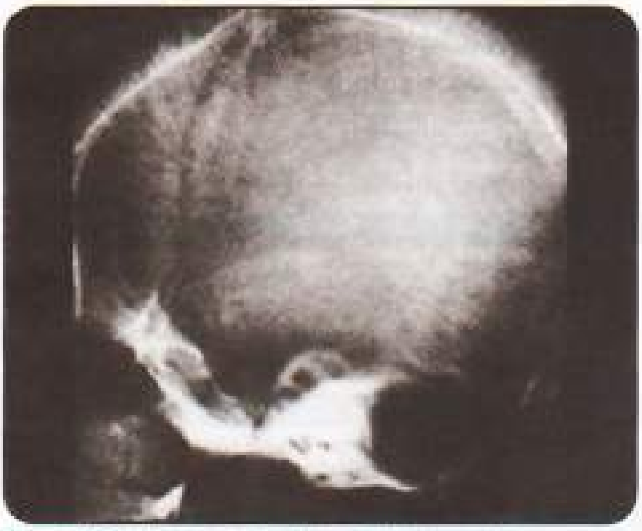


Figure 16.3: Hair-on-end pattern in thalassemia.

Table 16.2: Laboratory studies differentiating iron deficiency anemia and thalassemia.

	Iron deficiency anemia	**Thalassemia**
Hemoglobin	Decreased	Decreased
MCV	Decreased	Decreased
RDW	Increased	Normal or minimally increased
RBC	Decreased	Normal-increased
Serum ferritin	Decreased	Normal
Total iron binding capacity	Increased	Normal
Transferrin saturation	Decreased	Normal
FEP	Increased	Normal
Transferrin receptor	Increased	Normal
Reticulocyte hemoglobinconcentration	Decreased	Normal

FEP (Free Erythrocyte Protoporphyrin), MCV (Mean Corpuscular Volume), RBC (Red Blood Cell Count), RDW (red cell distribution width).

Complications

Iron overload

- Cardiomyopathy
- Heart failure
- Arrhythmias
- Hepatic fibrosi/cirrhosis
- Endocrinopathy:
    - Hypothyroidism
    - Hypoparathyroidism
    - Diabetes mellitus
    - Hypogonadism
    - Delayed puberty

Bone disease

- Osteopenia
- Osteoporosis

(These complications can cause persistent backache, scoliosis, fractures and cord compression)

Infections

- Thalassemia patients are prone to infections caused by HBV, HCV and Yersinia enterocolitis.

Hypercoagulopathy: This can lead to

- Pulmonary embolism
- Cerebral ischemia
- Deep venous thrombosis

Alloimmune and RBCs autoimmunization

- Transfused patients might develop anti-RBC antibodies, allo-antibodies or auto-antibodies that may cause hemolytic transfusion reaction.

Management

General

- Goals of therapy are to maintain a normal hemoglobin level and to prevent iron accumulation and promote iron excretion.

Transfusion therapy

- Packed RBCs transfusion (15–20 ml/kg) should be given every 4–8 weeks to maintain hemoglobin above 10 g/dl (hypertransfusion) or above 12 g/dl (super-transfusion).
- The total amount of packed cells required is calculated by the formula:
    - Desired Hb level–present Hb level x weight in kg x 3
    - Each unit of blood contains 200 mg of iron and excessive transfusions result in hemosiderosis.

Chelation therapy

- Deferoxamine (Desferal), 20–60 mg/kg sub-cutaneously over 8 hours by an infusion pump for a minimum of 5 nights/week. Or give 50 mg/kg with each transfusion through a separate tubing over 8 hours. Its half-life is less than 30 minutes.
- Deferoxamine is initiated between 4–5 years of age when serum ferritin is greater than 1000 ng/ml and transferrin is >50% saturated.
- Side effects of deferoxamine are dizziness, peripheral neuropathy, hearing and visual disturbances, and cataracts.
- **Oral iron chelator**
    - Deferasirox: Its half-life is 16 hours and available in dispersible tablet. Its dose is 20 mg/kg once daily. Side effect is GIT upset and proteinmia.
    - Deferiprone (Asunra). It is rapidly absorbed. A dose of 75 mg/kg/day divided in three doses, each given one hour before meal is usually satisfactory. Serious side effects are agranulocytosis and arthropathy. In long term, deferiprone may not provide adequate control of body iron. Its half-life is 3 hours.

Ascorbic acid

- Ascorbic acid supplements 50–100 mg/day to increase urinary excretion of iron.

Folic acid

- 5 mg daily is given.

Splenectomy

- Indicated when:
    - There is hypersplenisim.

  - Packed RBCs requirements exceed >250 ml/kg/year.
- It is done after 5 years of age.
- Prophylactic penicillin, H. influenzae and pneumococcal vaccine are recommended to prevent fulminant sepsis.

Bone marrow transplantation

- Hematopoietic stem cell transplantation from an HLA compatible sibling has been used as a cure of homozygous beta-thalassemia.
- It is successful in young children without iron over load and hepatomegaly.

Gene therapy

- Gene therapy will be the ultimate treatment for providing a lifelong cure of thalassemia, in near future.
- Other approaches include repairing definitive genes or supporting selective genes, e.g. supporting a gene production in β-thalassemia.

Stimulation of fetalhemoglobin synthesis

- Hydroxyurea: It helps in the induction or reactivation of gamma globin synthesis, which binds alpha chains to produce fetalhemoglobin. A higher fetalhemoglobin may improve overall hemoglobin production and reduce ineffective erythropoiesis.
  - Hydroxyurea (capsule Hydrea) is used in daily dose of 10–20 mg/kg varying from 4–30 weeks. It is well tolerated and has side effects like leukopenia and thrombocytopenia.
- Recombinant erythropoietin increases recruitment of progenitor cells, some of which are more gamma-globin chains.

Prognosis

- It depends upon liver and cardiac iron overload, and endocrine dysfunction.
- Death due to congestive heart failure usually occurs within the first few years of life unless the patient is supported with blood transfusions.
- Quality of life has been improved by super-transfusions and chelation.
- Bone marrow transplantation is curative.

Prevention

- Genetic counseling for carriers

Genetic counseling and inheritance

- The probability of an offspring of heterozygous parents having the thalassemia major is 1 in 4 (25%) in each pregnancy while 2 in 4 (50%) are likely to have thalassemia minor and 1 in 4 (25%) are expected to be normal in each pregnancy.

Antenatal diagnosis

- FetalDNA, may be obtained by either chorionic villus sampling in first trimester or by amniocentesis in second trimester.
- By fetal DNA analysis diagnosis can be made before the 10th week of gestation.

HEREDITARY SPHEROCYTOSIS

CASE

A 5-year-old girl presents with a four-day history of ***fever*** and ***increasing jaundice***. There is past history of neonatal jaundice. There is past history of splenectomy in a family member. On examination, she is pale and has jaundice. There is no lymphadenopathy or hepatomegaly. She has ***splenomegaly***. On laboratory investigations, ***hemoglobin is 4.6 g/dL***, numerous ***spherocytes*** on peripheral smear. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) are normal.

- Hereditary spherocytosis is a common cause of hemolysis and inherited hemolyticanemia.
- It is the most common inherited abnormality of the Red Blood Cell (RBC) membrane.

Etiology

- Hereditary spherocytosis is usually an autosomal dominant disorder (75%). Remaining cases are autosomal recessive or new mutations.
- The most common molecular defects are abnormalities of spectrin or ankyrin, which are major components of the cytoskeleton responsible for RBC shape.
- The decreased deformability of the spherocytic RBCs impairs cell passage from the splenic cords to the splenic sinuses. Spherocytic RBCs are destroyed prematurely in the spleen.

Clinical findings

- In the newborn, due to hemolysis, there is anemia and hyperbilirubinemia.
- Older children present with pallor, jaundice, fatigue, and exercise intolerance.
- Severe cases may have marked expansion of the diploë of the skull and the medullary region of other bones.
- Spleen is usually enlarged, and pigmentary (bilirubin) gallstones may form at 4–5 years of age.
- The erythroid marrow failure may result in severe anemia, high-output heart failure, hypoxia, cardiovascular collapse, and death.

Diagnosis

- The diagnosis of hereditary spherocytosis is apparent clinically from:
  - Family history
  - Splenomegaly
  - Indirect hyperbilirubinemia
  - Decreased haptoglobin
  - Presence of gallstones on ultrasonography

- The hemoglobin level usually is 6–10 g/dL.
- RBCs on the blood film vary in size and include reticulocytosis and spherocytosis. The presence of spherocytes in the blood can be confirmed with an **osmotic fragility test**.
- Erythroid hyperplasia is present in the marrow aspirate or biopsy.
- Marrow expansion may be apparent on routine X-ray examination of bones.

Differential diagnosis

- Other causes of spherocytosis:
    - Isoimmune and autoimmune hemolysis
    - Isoimmunehemolytic disease of the newborn, particularly due to ABO incompatibility

Management

- Splenectomy (after age 5–6 years) is curative treatment of hereditary spherocytosis.
- Folic acid, 1 mg daily, should be administered to prevent deficiency and the resultant decrease in erythropoiesis.
- Vaccines such as pneumococcus, meningococcus, and *Haemophilusinfluenzae* type b, should be administered before splenectomy.
- Prophylactic oral penicillin V (250 mg twice daily up to adulthood) should be administered after splenectomy.
- Partial splenectomy may be useful in children younger than 5 years of age.

Prognosis

- Splenectomy eliminates signs and symptoms and reduces the risk of cholelithiasis.

SICKLE CELL ANEMIA

CASE

A 2-year-old child presents with painful swelling of the hands and feet (***dactylitis***), pallor (***anemia***) and right-sided weakness (stroke). Laboratory evaluation reveals hemoglobin of 9 g/dL. Hemoglobin electrophoresis shows presence of high levels of HbS.

- Sickle cell anemia is a hemoglobinopathy causing hemolyticanemia.
- On screening, hemoglobin may be HbSS, HPFH (HbS hereditary persistent fetalhemoglobin or HbSβ-thalassemia, if at least 50% of the hemoglobin is HbS

Pathogenesis

- There is an abnormal autosomal gene that substitutes valine for glutamic acid in the 6th position of the beta-globin chain.
- Under conditions of hypoxia, the hemoglobin aggregates and RBCs becomes sickle shape.
- There is shortened red blood cell survival (hemolyticanemia).
- There is microvascular obstruction, which leads to tissue ischemia and infarction.

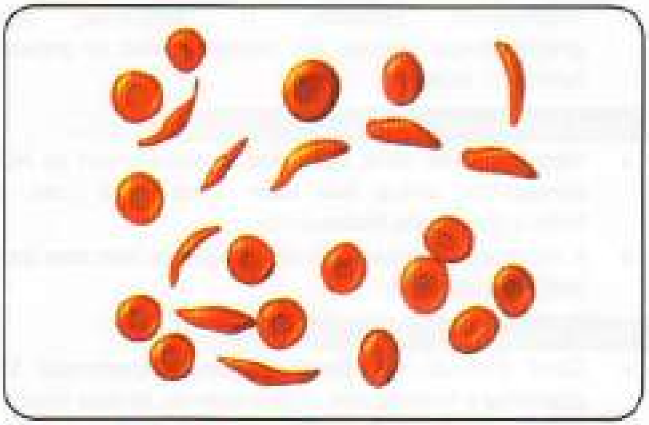


Figure 16.4: Blood picture in sickle cell anemia.

Clinical findings

- In the **asymptomatic period**, the high levels of HbF during the first few months of postnatal life protect the patient.
- The **earliest clinical manifestations** may occur at 4–6 months of age. These include:
    - Dactilitis: Symmetric, painful swelling of the dorsal surfaces of the hands and feet (hand-foot syndrome). This is caused by avascular necrosis of the bone marrow of the metacarpal and metatarsal bones.
    - Progressive anemia
    - Jaundice
    - Splenomegaly
- A **splenic sequestration crisis** is a life-threatening problem of spleen. The spleen is rapidly enlarged with trapping of blood and hypovolemia with drop in hemoglobin of at least 2 gm/dL . This can lead to hypovolemic shock and death.
- Fever: Patients are very susceptible to **overwhelming infection**, particularly with encapsulated bacteria (pneumococci, hemophilus influenza) and salmonella (septicemia, osteomyelitis). Spleen does not perform its filtering function for microorganisms.
- **Aplastic crisis** can occur at any age. There is suppression of erythropoiesis in response to viral infection such as parvovirus-B19.
- **Vaso-occlusive episodes** can involve any tissue. There may be abdominal pain, bone pain, Cerebrovascular Accidents (CVA), pulmonary infarction, hepatopathy, or hematuria.
    - The acute chest syndrome is characterized by fever, rales, pleuritic chest pain, and pulmonary infiltrates on chest radiography.
    - Repeated vaso-occlusive episodes in the spleen lead to infarction, fibrosis, and regression. Spleen is not palpable after the age of 5 years.
- Late manifestations are:

  - Long-term consequences of chronic anemia
  - Tissue hemosiderosis
  - Tissue infarction
  - Gallstones
  - Leg ulcers
  - Renal damage
  - Aseptic necrosis of the long bones

Diagnosis

- Children with sickle cell anemia (homozygous sickle cell disease) show a hemoglobin level of 7–10 g/dL.
- The baseline reticulocyte count is elevated markedly.
- Peripheral blood smear shows the characteristic sickle cells as well as numerous target cells.
- Hemoglobin electrophoresis is always necessary to accurately identify a sickle disorder.

Complications

- Repeated tissue ischemia and infarction causes damage to every organ system.
- Patients who require multiple transfusions may develop transfusion-related hemosiderosis and red cell alloantibodies.

Management

- Protect the patients from overwhelming gram-positive sepsis.
- Prevention of vaso-occlusive episodes involves the avoidance of dehydration, hypoxia, chilling, and acidosis.
- Treatment of vaso-occlusive episodes:
  - Analgesics for pain
  - Transfusion with packed red blood cells
  - For repeated attacks a chronic transfusion program to keep HbS level at less than 30%
- A severe aplastic crisis requires transfusion with packed RBCs.
- Hydroxyurea: Use of agents that elevate HbF levels is indicated because HbF correlate inversely with disease severity, painful episodes, dactylitis, stroke, etc. Its dose is 15–20 mg/kg once daily with 5 mg/kg increment every 8 weeks with a maximum of 35 mg/kg/day.
- Hematopoietic stem cell transplantation is another option.

Prognosis

- Early identification of infants with sickle cell disease and comprehensive care reduces mortality in childhood. Most patients now live well into adulthood, but may develop complications.

MACROCYTIC MEGALOBLASTIC ANEMIA

- Megaloblasticanemia is a macrocytic anemia caused by deficiency of vitamin B_{12} (cobalamin), folic acid, or both.
- Megaloblasticanemia is characterized by abnormal morphology and maturation of erythrocytes.
- The nucleated erythrocytes have an open, finely dispersed arrangement of chromatin and asynchronous maturation of nucleus and cytoplasm.
- There is disordered synthesis of DNA, and megaloblastic cells have increased amounts of RNA relative to DNA.

Vitamin B_{12} deficiency

CASE

A 4-year-old girl presents with ***pallor*** and lethargy. She is on ***vegan diet*** (a diet excluding all animal products including eggs, milk, and milk products, as well as meat and fish). Hemoglobin of 7.6 g/dL, an MCV of 105 fL. Blood smear shows megaloblasticanemia.

It is caused by:

- Dietary insufficiency in breastfed infants of mothers who are strict vegetarians or who have pernicious anemia.
- Intestinal malabsorption: It occurs in Crohn's disease, chronic pancreatitis, bacterial overgrowth of small intestine, infection with Diphyllobothriumlatum (fish tapeworm), or after surgical resection of the terminal ileum.
- Pernicious anemia (a rare cause of malabsorption of vitamin B_{12} due to deficiency of intrinsic factor).
- Deficiency of vitamin B_{12} due to inborn errors of metabolism (transcobalamin II deficiency, methylmalonicaciduria).

Folic acid deficiency

CASE

A 6-month-old infant presents with poor weight gain and ***pallor***. His diet consists only of ***goat milk*** and no solid diet (goat milk contains little folate). On clinical examination, he is tired and is tachycardiac.

It is caused by:

- Inadequate dietary intake or ingestion of goat's milk
- Malabsorption (celiac disease)
- Increased folate requirements (rapid growth, chronic hemolyticanemia)
- Anticonvulsant medications (e.g. phenytoin, phenobarbitone), and cytotoxic drugs (e.g. methotrexate)
- Prematurity (low body stores of folate)

Clinical findings

In infants

- Pallor
- Mild jaundice due to ineffective erythropoiesis

- Tongue is smooth and beefy red
- Irritability with poor feeding

In older children

- Pallor
- Paresthesias, weakness, or an unsteady gait
- Decreased vibratory sensation and proprioception

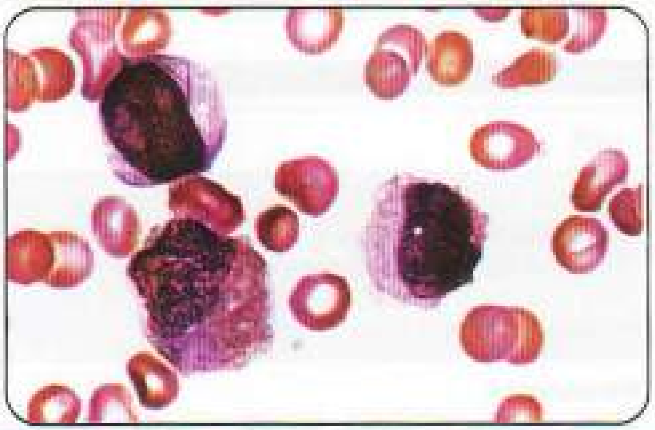


Figure 16.5: Peripheral blood film in folic acid deficiency.

Diagnosis

- Increased **Mean Corpuscular Volume** (MCV) and **Mean Corpuscular Hemoglobin** (MCH).
- Numerous macro-ovalocytes with anisocytosis and poikilocytosis on **peripheral blood film**.
- **Neutrophils** are large with hypersegmented nuclei.
- **WBC count** and **platelet count** are normal with mild deficiencies but in severe cases may be decreased.
- **Bone marrow** shows erythroid hyperplasia with large erythroid and myeloid precursors. Nuclear-cytoplasmic dissociation and ineffective erythropoiesis is seen.
- **Serum indirect bilirubin** concentration may be slightly raised.
- In vitamin B_{12} deficiency, there is low **serum vitamin B_{12} level.** Serum levels of intermediate metabolites (methylmalonic acid and homocysteine) are more helpful for diagnosis.
- In folic acid deficiency, **red cell folate level** is decreased.

Treatment

- **Folic acid** (1–5 mg/day orally for 3–4 weeks) or **vitamin B_{12}** (1 mg IM for 2–4 days) is given according to the cause of the megaloblasticanemia.
- Children at risk for the development of folic acid deficiencies (premature infants and those with chronic hemolysis) are given folic acid prophylactically.
- Folic acid should not be given in a patient with megaloblasticanemia until a diagnosis of folate deficiency has been made. Folic acid is contraindicated in vitamin B_{12} deficiency.
- **Blood transfusion** is given if necessary.

ACQUIRED APLASTIC ANEMIA

CASE

A 7-year-old child presents with ***fever*** for one week and occasional ***bleeding*** from nose. On examination, he is ***pale***. There is ***no hepatosplenomegaly***. On investigation, ***hemoglobin*** is 5.5/dl (***low***), ***WBC*** 3000/mm^3 (***low***), ***platelets*** 35,000/mm^3 (***low***) and ***reticulocytes*** 0.5% (***low***).

- Acquired aplastic anemia is characterized by peripheral pancytopenia with a hypocellular bone marrow (less than 30% cellularity).
- About 50% of the cases in children are idiopathic.
- Aplastic anemia is due to a reduction in the number of pleuripotent stem cells. Failure of one cell line may occur resulting in isolated deficiencies such as the absence of red cell precursors in pure red cell aplasia.

Table 16.3: Classification of aplastic anemia.

Camitta's classification
• Mild/mod (hypoplasticanemia) ANC 500–1500 Platelet count-20k-1 lac
• Severe aplastic anemia* ANC <500 Platelet count-<20k
• Very severe* ANC <200
* In addition <25% bone marrow cellularity

- **Severe aplastic anemia** is defined as a condition in which two or more cell components have become seriously compromised (i.e. an Absolute Neutrophil Count (ANC) <500/mm^3, a platelet count <20,000/mm^3, a reticulocyte count <1% after correction for the hematocrit) in a patient whose bone marrow biopsy is hypocellular.

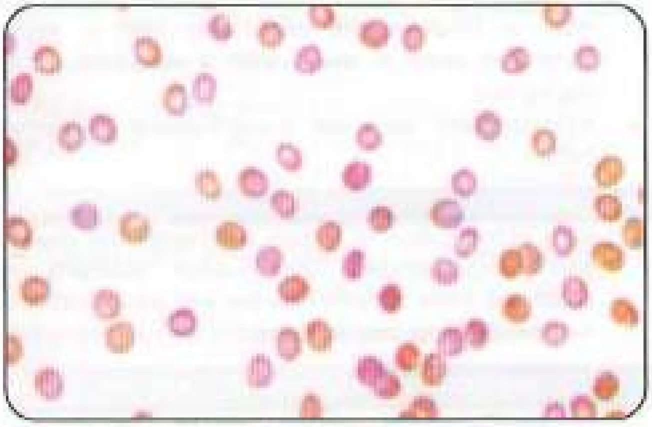


Figure 16.6: Peripheral blood film in aplastic anemia. There are occasional macrocytes and absence of white blood cells and platelets.

Etiology

1. Idiopathic
2. Secondary
   - Drugs and chemicals:
     - Cytotoxic agents
     - Chloramphenicol
     - Phenylbutazone
     - Sulfonamides
     - Insecticides
     - Novalgin
     - Sodium valproate
     - Cimetidine
     - Gold salts
   - Viruses:
     - Ebstein-Barr virus (infectious mononucleosis)
     - Hepatitis virus
     - Human Immunodeficiency Virus (HIV)
     - Parvovirus - 19
   - Pre-leukemia
   - Radiation
   - Thymoma

Pathophysiology

- Aplastic anemia is due to the destruction or dysfunction of the pleuripotent stem cell (progenitor of erythrocytes, platelets, monocytes, and granulocytes).
- Every third patient of aplastic anemia has an autoimmune disorder that is mediated through an inhibitory process involving T lymphocytes.
- Many drugs, infections, and environmental factors are associated with aplastic anemia. Ionizing radiation, some chemicals and many anti-neoplastic drugs are directly toxic to the bone marrow and produce bone marrow hypoplasia in a dose-dependent manner.
- Some drugs produce an idiosyncratic reaction. These include some antibiotics (e.g. chloramphenicol), anti-inflammatory agents and anti-convulsants. About 50% of the drug-related aplastic anemia is due to chloramphenicol.

Clinical findings

- Signs and symptoms of aplastic anemia depend on the degree of pancytopenia.
- Acquired pancytopenia is usually characterized by anemia, leukopenia, and thrombocytopenia with the consequent pallor, increased risk of fatigue, cardiac failure, infections, and bleeding.
- Hepatomegaly, splenomegaly, and lymphadenopathy are not present.

Diagnosis

- **Anemia** is usually normocytic, with a low **reticulocyte count** (<1%).
- **White blood cell count** is low, with a marked neutropenia (at times below 1500/mm^3).
- **Platelet count** is typically below 50,000/mm^3, and frequently below 20,000 mm^3.
- **Bone marrow aspiration and biopsy** are essential to diagnose and show hypocellularity (a decrease in the erythroid, myeloid and megakarycytes series), often marked with the marrow space replaced with fat. The presence of more than 70% lymphocytes has poor prognosis.

Differential diagnosis

- Acute leukemia
- Hypersplenism
- Sepsis or DIC

Complications

- Infections
- Hemorrhage
- Complications associated with therapy

Management

- Comprehensive **supportive care.**
- **Remove exposure** to hazardous drugs or toxins.
- All febrile illnesses require prompt evaluation and usually **parenteral antibiotics.**
- **Packed red blood cells** should be transfused for anemia.
- **Platelet transfusions** are given for bleeding.
- **Bone marrow transplantation** is the treatment of choice for patients with severe aplastic anemia when an HLA-compatible sibling donor is available. Survival appears to be superior when bone marrow transplantation is performed early.
- The best alternative to bone marrow transplantation for patients without and HLA-identical sibling is **immunosuppression**, usually with **Anti-Lymphocytic Globulin (ALG), cyclosporin, and corticosteroids**. This combination therapy results in a complete or partial remission in 65% of cases.
  - Methyl prednisolone alone is given in a single dose of 5 mg/kg/day PO or IV for 8 days followed by single dose of 1 mg/kg/day for 6 days. Taper dose in next 6 days and then discontinue. Response rate to steroids alone is 25%.
  - ALG is given in a dose of 40 mg/kg/dose as a continuous IV infusion over 12 hours with methyl prednisolone 1 mg/kg/day IV for 4 days. ALG alone gives 50% partial or complete response rate.
  - Cyclosporin is given orally in a dose of 8 mg/kg/day for initial 14 days then 15 mg/kg/day. Continue treatment for a minimum of 3 months.
- One or more **hematopoietic Colony Stimulating Factors** (CSF) may also be used.
- **Other treatment modalities** for aplastic anemia are:
  - Intravenous Immunoglobulins (IVIG)
  - Anti-thymocytic Globulin (ATG)
  - Recombination human IL-3
  - Gene therapy

Prognosis

- The prognosis for patient with severe aplastic anemia is extremely poor:
  - If bone marrow transplantation is not available
  - If immunosuppression is not effective
- In such cases, patients often die of infection or hemorrhage within 6–12 months after diagnosis.
- Children treated early with bone marrow transplantation from an HLA-identical sibling have a long-term survival rate greater than 80%.
- Many treated with immunosuppressive therapy get sustained complete remission.
- However, recent studies show that both therapies are associated with an increased risk of myelodysplastic syndromes, acute leukemia, and other malignancies in long-term survivors.

ENZYMATIC DEFECTS

G6PD DEFICIENCY

CASE

A 4-year-old previously well boy develops ***pallor***, ***dark urine*** and rapid-onset ***jaundice***. There is no history of exposure to a jaundiced person or to any toxins. He is ***taking trimethoprim-sulfamethoxazole*** for otitis media. Vital signs are normal. Hemoglobin is 7 g/dL with a normal platelet and white blood cell count. Total bilirubin is 4 mg/dL. ***Bilirubin*** is ***predominantly unconjugated*** and the ***reticulocyte count is 12% (raised)***. Urine shows hemoglobin +++ and RBC >20/hpf.

- Deficiency of G6PD is the most common red cell enzyme defect that causes hemolyticanemia.
- The disorder has X-linked recessive inheritance.
- Glucose-6-phosphate dehydrogenase (G6PD) deficiency causes two types of hematologic conditions:
  - Acute condition is common and is manifested by hemolytic episodes which are induced by infection or some drugs.
  - Chronic condition is rare and is a non-spherocytichemolyticanemia.

Pathophysiology

G6PD-deficient cells do not generate an amount of reduced glutathione

↓

Red blood cells are not protected from oxidant agents

↓

Exposed sulfhydryl groups of hemoglobin are oxidized

↓

Denaturation of hemoglobin

↓

Heme and globin moieties dissociate (hemolysis)

↓

Globin precipitating as Heinz bodies

↓

Damaged red blood cells are then removed by the reticuloendothelial system

↓

Severely damaged cells may lyse intravenously

- Hemolysis occurs only if the patient is exposed to oxidant drugs. Degree of hemolysis varies with:
  - The drug
  - The amount ingested
  - The severity of the enzyme deficiency in the patient
- In most cases, enzyme deficiency is due to the instability of the abnormal enzyme, and older cells are thus more deficient than younger ones.
- Synthesis of red-cell G6PD is determined by genes on the X-chromosome thus causing disease more frequently in males.

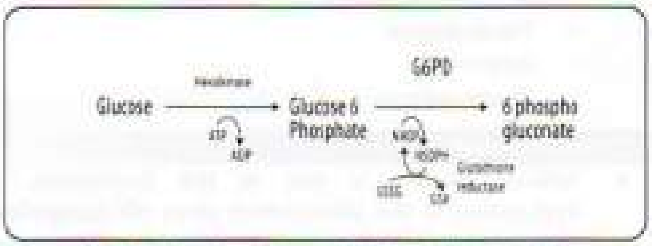


Figure 16.7: Pathophysiology of G6PD deficient cells

Agents precipitating hemolysis in glucose-6-phosphate dehydrogenase deficiency

- Medications:
  - Sulfonamides
  - Dapsone
  - Trimethoprim-sulfamethoxazole.
  - Nalidixic acid
  - Chloramphenicol
  - Nitrofurantoin
  - Primaquine
  - Chloroquine
- Chemicals:
  - Vitamin K analogs
  - Methylene blue
  - Probenecid
  - Acetylsalicylic acid
  - Naphthalene (moth balls)
- Illness:
  - Diabetic acidosis
  - Hepatitis
  - Sepsis

Clinical findings

- Neonates with G6PD deficiency may have hyperbilirubinemia.
- Older children with G6PD deficiency are asymptomatic and appear normal between episodes of hemolysis.

- The triggering event is the intake of drugs such as antipyretics, or anti-malarials.
- About 24–48 hours after the ingestion of oxidant substance pallor, jaundice, hemoglobinemia and hemoglobin-uria develops. There is intravascular hemolysis. Sometimes, there may be cardiovascular compromise.
- Hemolytic episodes may also be triggered by infection.

Investigations

- **Hemoglobin level** is reduced (may be as low as 2–5 g/dl.)
- **Urine examination** reveals hemoglobinuria. (coca colored urine)
- **Bilirubin level** is raised.
- **Peripheral blood smear** may reveal Heinz bodies in the first 3–4 days of illness.

Diagnosis

- History of previous episode
- Family history
- Demonstration of low G6PD levels (below 15%). Immediately after hemolysis, the level may be normal, because of presence of young red cells and reticulocytes, which have normal G6PD activity. Re-testing in a few weeks may confirm the diagnosis.

Management

- Prevention of hemolysis by **avoiding (or discontinuing) oxidant drugs**.
- Infections are treated and **antibiotics** are given when appropriate.
- Most episodes of hemolysis are self-limiting.
- After hemolysis has occurred, **supportive therapy** is given.
- **Blood transfusion** in case of severe hemolysis.

Prognosis

- Most cases are mild and self-limiting.
- With severe hemolysis however, death may occur.

FANCONI ANEMIA

CASE

A 5-year-old child presents with ***pallor*** and ***hyperpigmentation***. He has ***bifid thumb*** and numerary digits.

- Pancytopenia refers to a reduction below normal values of all 3 peripheral blood lineages: leukocytes, platelets, and erythrocytes.

Etiology

- Fanconianemia is inherited in an autosomal recessive manner.
- Patients have typical physical anomalies and abnormal hematologic findings, the classic phenotype (39% of cases).
- Approximately 75% of patients are 3–14 years of age at the time of diagnosis.

Pathology

- All patients have abnormal chromosome fragility.
- An inability of the Fanconi cell to remove oxygen-free radicals, resulting in oxidative damage, is a contributing factor in the pathogenesis.

Clinical findings

- Pancytopenia (all cell lines)
- Microcephaly
- Absent thumbs
- Café-au-lait spots
- Cutaneous hyperpigmentation
- Short stature
- Upper limb abnormalities (thumbs, hands, radii, ulnas)
- Hypogonadal and genital changes (mostly male)
- Other skeletal findings (head/face, neck, spine)
- Eye/lid/epicanthalfold anomalies
- Renal malformations (horseshoe or absent kidney)
- Ear anomalies (external and internal), deafness
- Hip, leg, foot, toe abnormalities
- Gastrointestinal/cardiopulmonary malformations
- Chromosomal breaks
- Leukemic transformation

Diagnosis

- High MCV (Mean Corpuscular Volume).
- High HbF (FetalHemoglobin).
- Marrow failure (severe aplasia develops in most cases).
- Chromosome fragility (indicated by spontaneously occurring chromatid breaks, rearrangements, gaps, endo-reduplications, and chromatid exchanges). Cultured skin fibroblasts also show chromosome fragility.
- Prenatal diagnosis: Abnormal chromosome breakage can be tested on amniotic fluid cells or with chorionic villus biopsy.
- Elevated levels of serum α-fetoprotein (a rapid screening diagnostic test).

Complications

- Propensity for cancer

Associations

- Leukemia (AML)
- Congenital dislocation of hip
- Hypothyroidism
- Absent testes
- Mental retardation

Management

- Androgens

- Steroids
- Bone marrow transplantation
- Hematopoietic stem cell transplantation is the only curative therapy for the hematologic abnormalities
- Gene therapy

COAGULATION DEFECTS

NORMAL HEMOSTASIS

- Hemostasis is a complex process depending on interactions between the vessel wall, platelets and coagulation factors.

Vessel wall

- After an injury, there is an immediate reflex vasoconstriction of the injured vessel and adjacent vessels resulting in transient reduction of blood flow to the affected area.
- Due to the damage to the endothelium of the vessel, there is activation of platelets and coagulation.

Platelets

- There is platelet adhesion to collagen. This adhesion depends on platelets membrane receptors, glycoprotein Ia (which binds directly to collagen), and glycoprotein Ib (which binds to von Willebrand factor in the plasma). vonWillebrand factor in turn adheres to collagen.
- Following platelet adhesion, there is release of the contents of their cytoplasmic granules.
- Release of ADP leads to a conformational change in the fibrinogen receptor on the surface of adherent platelets allowing it to bind to fibrinogen. Fibrinogen then causes further platelet aggregation.
- Further platelet membrane receptors are exposed during aggregation, providing a surface for the interaction of coagulation factors.
- Platelets also release thromboxane A_2 that is a powerful vasoconstrictor.

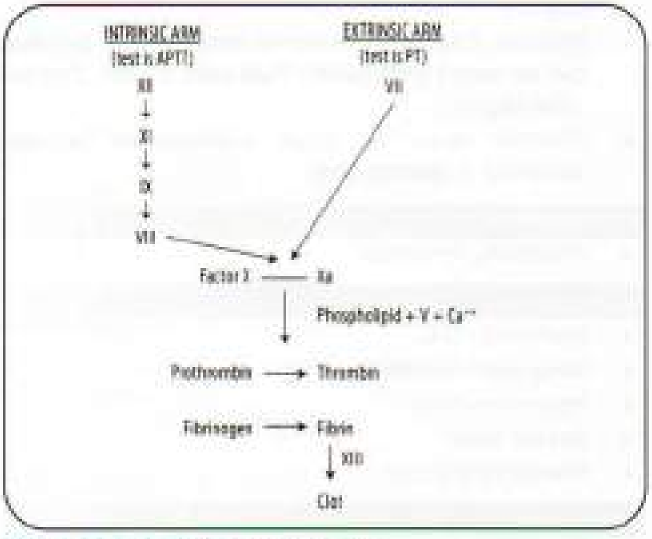


Figure 16.8: Coagulation pathway.

Coagulation

- The coagulation cascade involves a series of enzymatic reactions leading to the conversion of soluble plasma fibrinogen to fibrin clot. There are 'extrinsic' and 'intrinsic' coagulation pathways.
- Coagulation is initiated by tissue factor (expressed on the surface of perivascular endothelial cells), coming into contact with plasma after an injury. The complex of activated factor VII and tissue factor (TF: VII) activate factor X.
- Factor XII is thought to be activated by contact with the injured surface and then to initiate a series of reactions beginning with activation of factor XI and leading to activation of factor X.
- Activated factor X induces the conversion of prothrombin to thrombin.
- Thrombin hydrolyses the peptide bonds of fibrinogen, releasing fibrinopeptides A and B, and allowing polymerization between fibrinogen molecules to form fibrin.
- Thrombin also activates factor XIII, which stabilizes the fibrin clot.

Investigations of bleeding disorders

- **Blood count and film** show the number and morphology of platelets and any blood disorder such as leukemia.
- **Prothrombin Time (PT):** It screens the clotting activity of factors II, V, VII, X, and fibrinogen. Normal PT is 16–18 seconds.
- **Activated Partial Thromboplastin Time (APTT):** It screens clotting activity of factors XII, XI, IX, VIII, X, V, II, fibrinogen, pre-kallikrein, and High-Molecular-Weight Kininogen (HMWK). Normal APTT is 30–50 seconds.
- **Platelet count, platelet function analyzer (PFA-100)**
- **Bleeding Time (BT):** It screens small vessel integrity, von Willebrand and platelet function.
- **Thrombin Time (TT):** It measures the generation of fibrin following conversion of prothrombin to thrombin as well as the anti-thrombin effect of fibrin-split products or heparin. Normal TT is about 12 seconds.
- **Fibrinogen level**
- **Factor assays** are used to confirm coagulation defects, especially where a single inherited disorder is suspected.

HEMOPHILIA A

CASE

A 4-year-old boy presents with ***recurrent episodes of bleeding***. Now, he has swollen left knee. There is no history of trauma. There is past history of severe bleeding after circumcision. Laboratory investigations show ***bleeding time (normal)***, PT (normal), ***APTT (raised)***, factor VIII:C (low), platelet count (normal).

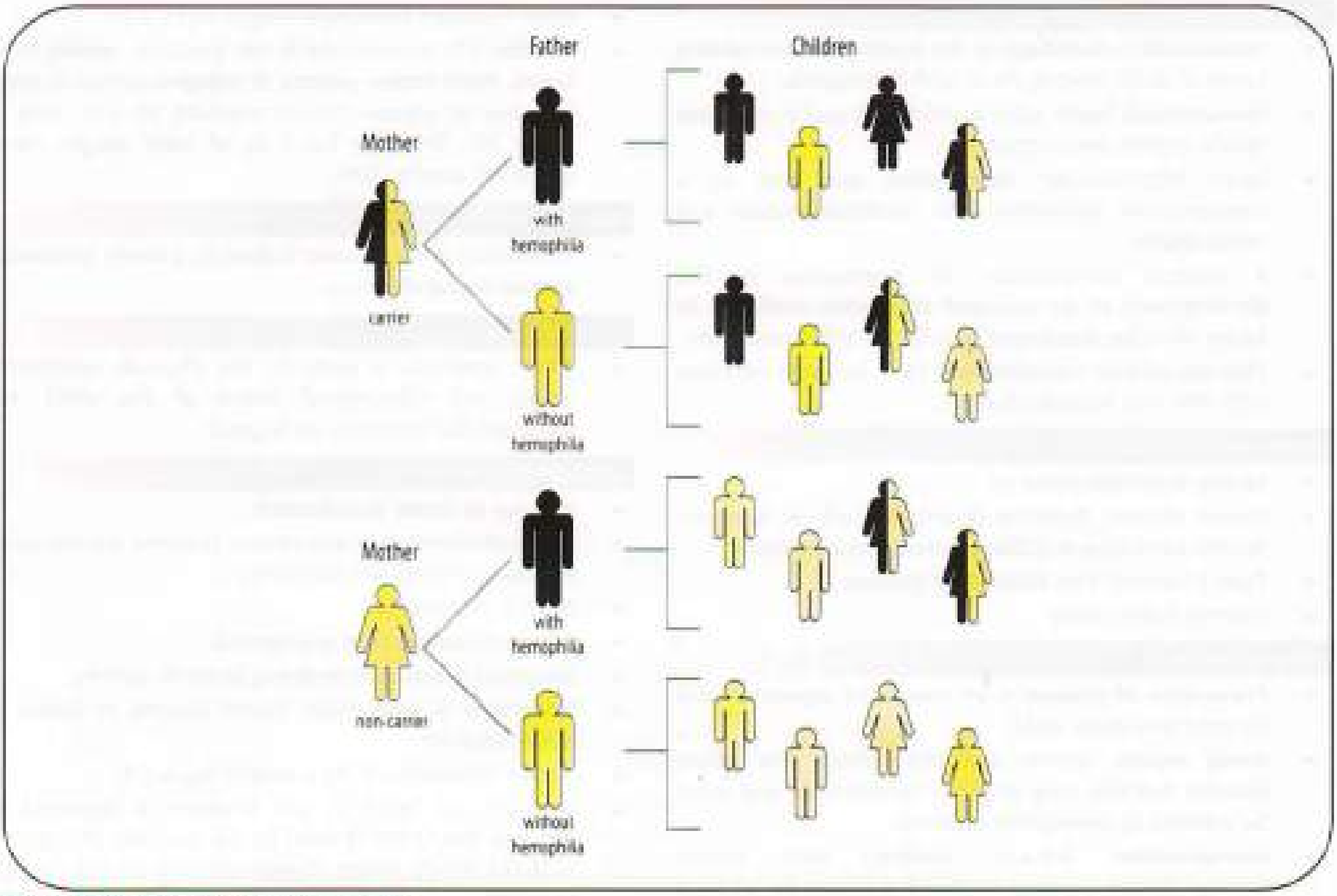


Figure 16.9: Inheritance in hemophilia.

- HemophiliaA (classic hemophilia) is a common severe inherited bleeding disorder due to decreased activity of factor VIII.
- Factor VIII activity is measured in units per ml, with 1 unit/ml equal to 100% of the factor activity found in 1 ml of normal plasma.
- The normal range for factor VIII activity is 50–150%.
- A positive family history is common.
- The disease occurs predominantly in males (1 in 5000) and is either inherited in an X–linked manner or is the result of a new mutation. One-third of cases are due to a new mutation.

Clinical findings

- **Severe factor VIII deficiency:**
  - Children with severe factor VIII deficiency are characterized by frequent spontaneous bleeding episodes involving skin, mucous membranes, joints, muscles, and viscera.
- They have less than 1% circulating factor VIII activity.
- **Mild factor VIII deficiency:**
  - Children with mild factor VIII deficiencybleed only at times of trauma or surgery.
  - They have 6%–30% factor VIII activity.
- **Moderate factor VIII deficiency:**
  - Those with moderate factor VIII deficiency have intermediate bleeding manifestations.
  - They have 1%-5% factor VIII activity.
- Because factor VIII does not cross the placenta, a bleeding tendency may be present in the neonatal period.
- In infants, excessive bleeding may occur after circumcision or injection.
- The most crippling complication (hallmark) of factor VIII deficiency is the tendency to develop recurrent hemarthroses causing joint destruction.

Diagnosis

- A **positive family history** is usually present.
- **APTT** (Activated Partial Thromboplastin Time) is **prolonged**, indicating a deficiency in the intrinsic pathway.
- **CT** (Clotting Time) is **prolonged**.
- **Bleeding time** and **PT** (prothrombin time) and **platelet count** are **normal**.
- The diagnosis is confirmed by finding **decreased factor VIII activity** with normal von Willebrand factor (VWF) activity.
- Carriers of hemophilia can be detected by demonstration of the ratio of factor VIII activity to VWF antigen and by molecular genetic techniques.

Complications

- **Intracranial hemorrhage** is the leading disease related cause of death among those with hemophilia.
- **Hemarthrosis** begin early in childhood and if recurrent results in joint destruction.
- Large intramuscular hematomas can lead to a compartment syndrome with resultant muscle and nerve death.
- A serious complication of hemophilia is the **development of an acquired circulating antibody to factor VIII** after treatment with factor VIII concentrate.
- **Therapy related complications** have included infection with HIV, and hepatitis B and C.

Differential diagnosis

- Severe thrombocytopenia
- Severe platelet function disorders, such as Bernard-Soulier syndrome and Glanzmannthrombasthenia
- Type 3 (severe) Von Willebrand Disease
- Vitamin K deficiency

Management

- **Prevention of trauma** is an important aspect of care for the hemophilic child.
- **Avoid aspirin**: Aspirin and other drugs that affect platelet function may provoke hemorrhage and must be avoided by hemophilic patients.
- **Immunization**: Because children with severe hemophilia are exposed to blood products throughout life, they should be immunized against hepatitis B virus.
- **General supportive care** is indicated for the hemorrhagic diathesis.
- **The aim is to normalize the factor VIII activity.**
- Some mild factor VIII-deficient persons may respond to **desmopressin acetate** (DDAVP), which is a synthetic vasopressin analog with minimal vasopressor effect.
- **Aminocaproic acid** and **tranexamic acid** are inhibitors of fibrinolysis that may be useful for oral bleeding.
- However, most patients require **administration of factor VIII concentrates** to achieve hemostasis. 15 units/kg of factor VIII raises plasma level by 30%, which is effective in most clinical circumstances. One unit of factor VIII activity is present in 1 ml of fresh-pooled plasma. Fresh frozen plasma (15 ml/kg) contains 0.7 units/ml, cryoprecipitate contains 75 units/bag, and factor VIII concentrate contains 250 units/vial. Cryoprecipitate contains fibrino-gen, factor VIII, and XIII. Plasma half-life of factor VIII (and VWF) is 12 hours.
- For life threatening bleeding, levels of 80–100% of normal factor VIII are necessary. For mild to moderate bleeding episodes (e.g. hemarthroses), a 40% level for factor VIII is appropriate. The dose can be calculated by knowing that 1 unit/kg body weight of factor VIII will raise the plasma level 2%. Therefore, dose of factor VIII can be calculated as follows:
- Dose = desired level (%) x weight (kg) x 0.5
- If factor VIII concentrate is not available, **whole fresh blood, fresh frozen plasma** or **cryoprecipitate** is used. One bag of cryoprecipitate contains 75–125 units of factor VIII. One bag for 5 kg of body weight raises factor VIII level to 50%.

Prevention

- Prevention of the disease is done by genetic counseling and antenatal diagnosis.

Prognosis

- When attention is given to the physical, emotional, social, and educational status of the child, the prognosis for a normal life is good.

HEMOPHILIA B

- It is due to factor IX deficiency.
- Mode of inheritance and clinical features are the same as those of factor VIII deficiency.
- APTT is prolonged.
- PT and thrombin time are normal.
- Diagnosis is based on assaying factor IX activity.
- Treatment is with fresh frozen plasma or factor IX administration.
- Dose = desired level (%) x weight (kg) x 1.4
- One unit of factor IX per kilogram is expected to increase the factor IX level by 1%. Half-life of factor IX is about 20–22 hours. Cryoprecipitate do not contain factor IX.

VON WILLEBRAND'S DISEASE

CASE

A 7-year-old girl presents with ***prolonged bleeding*** after epistaxis. She used to have similar episodes off and on. On examination, she is pale and has some bruises over shins. Rest of systemic examination is unremarkable. On investigations, hemoglobin 7 g/dl, ***platelets*** 180,000/m^2 ***(normal)***, ***bleeding time*** 11 minutes (***prolonged***), PT 15 seconds (control 13 seconds) (normal), APTT 38 seconds (control 35 seconds) (normal), factor VIII:C (decreased), ***ristocetin cofactor activity (decreased)***.

- Von Willebrand'sDisease(VWD) is the most common inherited bleeding disorder (1:100 to 1:10,000).

Pathophysiology

- Von Willebrand's Disease is a heterogeneous group of disorders involving primary defects or deficiencies in the VWF portion of the factor VIII complex.
- VWF is a glycoprotein synthesized by megakaryocytes and endothelial cells. It binds to endothelial surface and activates platelets and starts coagulation cascade.
- VWF serves as a carrier protein for factor VIII and also is a cofactor for platelet adhesion. Its deficiency may cause secondary deficiency of factor VIII causing

prolonged APTT. There are also variable deficiencies of factor VIII:C (the procoagulant component of factor VIII molecule). This causes coagulation disturbances.

- Abnormalities of VWF (Von Willebrand's factor) results in:
  - Decreased platelet adhesive-ness,
  - Impairment of agglutination of platelets in the presence of ristocetin.Ristocetin-induced platelet aggregation is impaired because platelets adhere to sub-endothelial connective tissue, and
  - Prolongation of the bleeding time.
- Von Willebrand's Disease is usually transmitted as an autosomal dominant trait. Rarely, transmission may be autosomal recessive.

Types

- There are three major types of Von Willebrand's Disease:
- **Type I:** There is mild to moderate quantitative deficiency of VWF.
- **Type II:** Due to qualitative defective function of VWF.
- **Type III:** Due to complete absence of VWF.

Clinical findings

- In Von Willebrand's Disease, there is a mild to moderate bleeding tendency, usually involving mucocutaneous surfaces.
- There may be epistaxis, increased bruisability, melena, menorrhagia, hemorrhage after dental extraction, or excessive bleeding after trauma or surgery.
- Hemarthrosis is an unusual presentation.
- Type III has severe epistaxis and or menorrhagia.

Diagnosis: (type 1)

- Platelet count–normal
- Bleeding time–prolonged
- Factor VIII–decreased
- VWF–decreased
- Ristocetin cofactor activity–decreased
- APTT is usually prolonged, depending on the level of VIII: C activity, but may be normal. PT is normal.
- There is no single test that can reliably diagnose VWD.

Management

- Treatment of VWD depends on the type of VWD present and on the reason for treatment.
- **Cryoprecipitate** contains intact VWF and is effective in treating most subtypes of Von Willebrand's Disease. Cryoprecipitate corrects the bleeding time for only a few hours.
- For mild to moderate bleeding in type I Von Willebrand's Disease is **Desmopressin Acetate** (DDAVP) is used. It causes release of VWF from endothelial cells. Effect of DDAVP on bleeding time is transient (about 3–4 hours). Dose is 0.3 mg/kg IV in 20–30 ml of normal saline given over 20–30 minutes. To assess response, bleeding time is measured before and 30 minutes after infusion. Desmopressin is ineffective in patients with type III Von Willebrand's Disease.
- To control oral, nasal or vaginal bleeding, **anti-fibrinolytic drugs** (e.g. aminocaproic acid) are useful.
- Type 1 VWD patients may be treated with desmopressin.
- Treatment of types 2 and 3 VWD requires VWF-containing concentrates similar to the treatment of hemophilia.

CONSUMPTIVE COAGULOPATHY (DIC)

CASE

A 9-year-old boy presents in emergency department because of ***fever***, ***bleeding*** and ***shock***. Laboratory findings shows a platelet count of 50,000/µL (***thrombocytopenia***), ***prolonged Prothrombin Time*** (PT) of 20s (control 11.5 s), ***prolonged Activated Partial Thromboplastin Time*** (aPTT) of 51 s (control 36 s), ***prolonged Thrombin Time*** (TT) of 13.7 s (control 10.5 s), and ***decreased factor VIII level*** of 14% (normal 38 to 178%).

- DIC (Disseminated Intravascular Coagulation) is an acquired pathologic process characterized by activation of the coagulation system. There is a combination of accelerated fibrinogenesis and fibrinolysis.
- In DIC, there is:
  - Thrombin generation
  - Intravascular fibrin deposition
  - Platelet consumption
- There is micro-thrombi formation, which are composed of fibrin and platelets. These micro-thrombi may produce ischemic tissue damage.
- There is activation of fibrinolytic system, producing plasma-mediated destruction of fibrin, fibrinogen, and other clotting factors (factor V, factor VIII).
- Split (degradation) products of fibrin-fibrinogen are formed and function as anti-coagulants and inhibitors of platelet function.
- Conditions triggering the DIC are:
  - Endothelial cell damage with endotoxins or viruses
  - Tissue destruction due to physical injuries or necrosis
  - Hypoxia due to acidosis
  - Ischemia and vascular changes due to shock and hemangiomas
  - Release of tissue procoagulants, e.g. in cancers

Clinical findings

- Diffuse bleeding tendency, e.g. hematuria, melena, purpura,petechiae, or persistent oozing from injection sites. Purpuric lesions are often symmetric and show sharply demarcated borders with a surrounding inflammatory reaction.

- Circulatory collapse
- Poor skin perfusion
- Early ischemic changes due to widespread micro-thrombi in the vascular bed of a variety of organs. Renal failure is common.
- Evidence of thrombosis (gangrene, purpurafulminans)
- Purpurafulminans represents a special systemic form of DIC. This is characterized by purpura and DIC, usually in association with viral, bacterial (e.g. meningococcal, streptococcal) or rickettsial infections or severe hypernatremia.

Diagnosis

- **PT and APTT** are prolonged.
- **Platelet count** is decreased (thrombocytopenia).
- **Reduction of clotting factors** particularly fibrinogen and factor II, V, and VIII. Protein C levels are reduced.
- Levels of **fibrin-fibrinogen split products** and d-dimers are increased. d-dimers is a test that measures the cross-linked fibrin degradation by-products.
- Microangiopathic changes in the erythrocytes are seen in **peripheral blood film**.

Differential diagnosis

- Bleeding due to liver disease, vitamin K deficiency and uremia.
- In fulminant hepatitis or advanced cirrhosis, there is decreased production of liver dependent coagulation factors and increased consumption of platelets and fibrinogen.
- Factor VII is markedly decreased in liver disease. In DIC, it is mildly decreased.
- Factor VIII may be normal or increased in liver disease. In DIC, it is decreased.

Management

- **Identification and treatment of underlying disorder.** If the triggering event can be treated, usually no other treatment is needed for bleeding tendency.
- **Replacement of coagulation factors and platelets.**
  - **Fresh frozen plasma** is given to replace decreased coagulation factors. Dose is 10–15 ml/kg, and it will raise clotting factor activity by about 10–15%.
  - **Cryoprecipitate** provides fibrinogen and factor VIII.
  - **Platelet concentrate** is given to replace platelets. In neonates, 10 ml of platelet concentrate/kg will raise the platelet count by 75,000–100,000/ml. In older children, dose is one bag/5 kg. One unit/m^2 of platelets concentrate will increase platelet count by about 20,000/µL.
  - Minimum levels to control bleeding are:

    Platelet count: >40,000/µl
    PT: <16 seconds
    Fibrinogen level: >100 mg/dl

- **Anti-coagulant therapy**: **Heparin** is particularly effective in purpurafulminants if initiated early in the illness.

DISORDERS OF PLATELETS

IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

CASE

A 3-year-old child develops bruising and ***generalized petechial rash***, more prominent over the legs. There is past history of respiratory infection about two weeks ago. There is ***no hepatosplenomegaly or lymphadenopathy***. Physical examination is otherwise normal. Laboratory investigations show a normal hemoglobin, hematocrit, and white blood count and differential. ***Platelet count*** is 15,000/µL (***low***).

- Idiopathic Thrombocytopenic Purpura (ITP) is an acquired hemorrhagic disorder in an otherwise well child characterized by:
  - Thrombocytopenia (defined as a platelet count less than 150,000/mm^3)
  - A purpuric rash
  - Normal bone marrow
  - Absence of signs of other identifiable causes of thrombocytopenia
- ITP is classified as acute or chronic.

Acute ITP

- Acute ITP is the most common bleeding disorder of childhood.
- It often follows infection with viruses such as rubella, varicella, measles, or Epstein-Barr virus.

Chronic ITP

- Chronic ITP is defined as the persistence of thrombocytopenia for more than one year from the initial presentation of signs and symptoms.
- Chronic ITP generally results from immune clearance of platelets, which generally have IgM or IgG on their surface.
- The spleen plays a major role by forming antibodies and by sequestering damaged platelets.

Incidence

- Incidence of symptomatic disease is approximately 3 to 8 per 100,000 children per year.
- Acute ITP is more prevalent among children younger than 10 years of age (maximum from 2–5 years), affects males and females equally.
- Chronic ITP affects adolescents more often than younger children, with females being affected more frequently than males.

Pathophysiology

- The destruction of platelets in ITP involves autoantibodies to glycoproteins normally expressed on platelet membranes.
- The spleen and other organs of the reticuloendothelial system subsequently destroy these antibody-coated platelets.
- In addition to increased immune-mediated destruction of platelets, there is evidence that platelet production in ITP is altered, especially in chronic ITP.
- Although the number of megakaryocytes in the bone marrow is normal or increased in ITP, plasma thrombopoietin levels, which are a measure of proliferation and maturation of megakaryocytic proginitors, are significantly decreased.

Clinical findings

- ITP is diagnosed largely on clinical findings.
- The typical clinical presentation is that of an otherwise healthy child who develops petechiae, multiple ecchymoses, easy bruising or a purpuric rash.
- Bleeding from mucous membranes, such as nose bleeding (epistaxis) or gum bleeding, is seen in about one third of cases.
- Other sites of bleeding include the gastrointestinal tract, vaginal mucosa, urinary tract, retina, and conjunctivae.
- In acute ITP, the onset of signs and symptoms often is preceded by a viral illness.
- Except for the manifestations of bleeding, findings on the physical examination are otherwise completely normal.
- In ITP, bruises are generalized and occur in areas not exposed to trauma.
- There is no hepatosplenomegaly and lymphadenopathy. The presence of either should raise the consideration of other disease, particularly leukemia.
- In chronic ITP, the presentation may be more insidious, and often the patient may be asymptomatic.

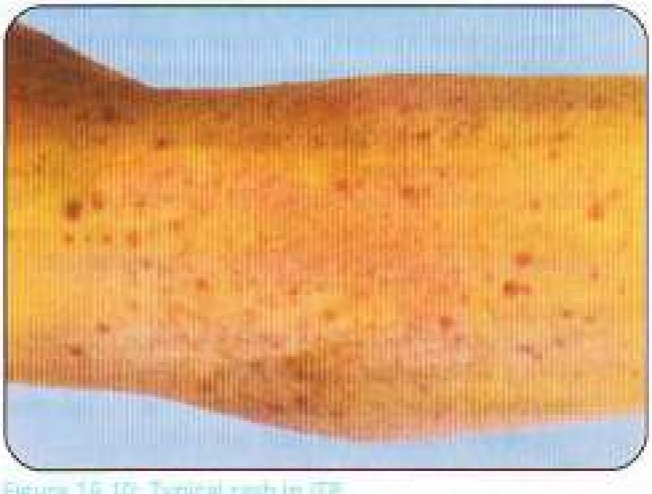


Figure 16.10: Typical rash in ITP.

Diagnosis

- Key to the laboratory diagnosis of acute ITP is the presence of a **low platelet count** (usually <50,000/mm^3 and often <10,000/mm^3), generally with normal values for age in all other cell lines.
- In about 15% of patients, **mild anemia** due to bleeding is present but red blood cell indices are normal.
- The **WBC count** and differential count are normal.
- If results of the complete blood count (CBC) are consistent with ITP, coagulation studies are not needed.
- The **Prothrombin Time** (PT) and **Activated Partial Thromboplastin Time** (APTT) are normal.
- **Bleeding time** (which is a direct test of platelet function) almost always is prolonged.
- On **bone marrow examination**, megakaryocytes usually are present in normal or increased numbers in acute ITP. Megakaryocytes may be larger than normal. Erythroid and myeloid cellularity is normal.
- **Platelet-associated IgG or IgM** or both may be demonstrated on the platelets or in the serum.

Differential diagnosis

- **Leukemia** (elevated WBC count, anemia, thrombocytopenia, and blast cells on peripheral smear; there may be hepatosplenomegaly or lymphadenopathy).
- **Aplastic anemia** (pancytopenia, severe neutropenia, low reticulocyte count)
- **DIC** (signs and symptoms of sepsis, elevated PT and APTT, decreased fibrinogen levels)
- **Lymphoma** (hepatosplenomegaly, lymphadenopathy)
- **SLE**

Management of acute ITP

Supportive measures

- Many children require no therapy.
- Restricting physical activity and avoiding trauma.
- Avoiding medications that suppress platelet production or alter their function (e.g. aspirin, heparin, chloramphenicol, sulfonamides, carbamazepine, valproic acid, digoxin, etc).
- Platelet transfusion may be given in emergency situations but are destroyed rapidly.

Pharmacological treatment

- It is much controversial as most cases of ITP are self-limited.
- The rationale for aggressive treatment of severe ITP at the time of diagnosis is to raise the platelet count to a level that decreases the risk of significant bleeding events.

Intravenous Immunoglobulin (IVIG)

- Currently, the mainstay of pharmacological management for acute ITP is IV immunoglobulins and corticosteroids. IVIG acts by blocking Fc receptors in

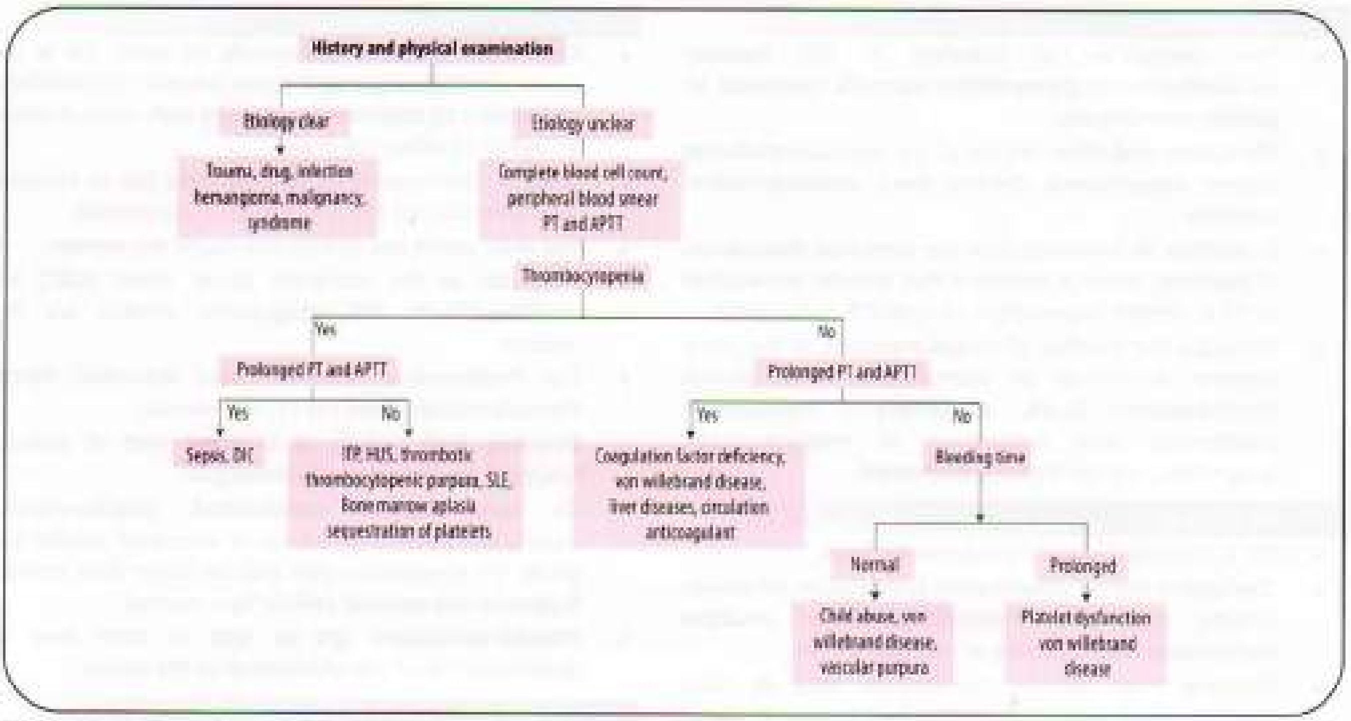

History and physical examination
Etiology clear
Etiology unclear
Trauma, drug, infection hemangioma, malignancy, syndrome
Complete blood cell count, peripheral blood smear PT and APTT
Thrombocytopenia
Yes
No
Prolonged PT and APTT
Prolonged PT and APTT
Yes
No
Yes
No
Sepsis, DIC
ITP, HUS, thrombotic thrombocytopenic purpura, SLE, Bone marrow aplasia sequestration of platelets
Coagulation factor deficiency, von willebrand disease, liver diseases, circulation anticoagulant
Bleeding time
Normal
Prolonged
Child abuse, von willebrand disease, vascular purpura
Platelet dysfunction von willebrand disease

Figure 16.11: Flow chart of differential diagnosis of thrombocytopenia.

the spleen and prevent antibody coated platelets being destroyed. By these agents, the mean time to raise platelet counts 20,000/mm^3 ranges from 24–72 hours after initiation of therapy.

- IVIG may be given in acute and chronic ITP. It is given even when patient is resistant to steroids.
- IVIG is given as 0.8–1.0 g/kg/day for 1–2 days.

Steroids

- Dose of prednisolone is 1–4 mg/kg orally in divided daily doses.
- Corticosteroid therapy is usually continued for short course (2 weeks) until a rise in platelet count to >20,000/mm^3 has been achieved to avoid the long-term side effects of corticosteroid therapy, especially growth failure, diabetes mellitus, and osteoporosis. This dose is then tapered and stopped.

Anti-Rh (D)

- It acts by forming RBC-antibody complexes which bind to macrophage Fc-receptors and prevent platelet destruction.
- It is less expensive than IVIG and has been shown to raise platelet counts effectively but slowly as compared to IVIG or steroids.
- However, it is useful only in patients who are Rh-positive, and mild hemolyticanemia can occur as a side effect.
- Approximately 80% of children with acute or chronic ITP respond well.
- Dose of Anti-Rh (D) is 50–75 µg/kg causes a rise in platelet count to >20,000/mm^3 in 80–90% of patients within 48–72 hours .

Management of chronic ITP

- As in acute ITP, the goal of management is to minimize the risk of significant bleeding.
- Patients should be directed to avoid activities that increase the risk of trauma and to avoid all medications that suppress platelet production and function.
- Patients should be evaluated for autoimmune disease as a greater percentage of patients who have features of chronic ITP have an underlying autoimmune disorder.
- Pharmacological approaches to the management of chronic ITP include steroids, IVIG, androgens, anti-Rh (D), recombinant human interferon-alpha-2b, and immunosuppressive agents used alone or in combination. Although all of these have been shown to induce a transient rise in platelet counts, none has demonstrated an ability to sustain a desirable platelet count, therefore, repeated treatments might be required.
- Because the majority of cases of chronic ITP remit either spontaneously or with treatment and because the associated morbidity and mortality are low, interventions are needed only when the platelet count is dangerously low or if the patient is symptomatic.

Splenectomy

- Splenectomy induces long-term remission (60–90%) in chronic steroid/IVIG-resistant ITP, but should only be considered after persistence of significant thrombocytopenia for at least one year.
- Those patients who demonstrated a significant, although transient, rise in platelet count after

treatment with either steroids or IVIG had a good response to splenectomy (i.e. they did not require any subsequent medical therapy for their thrombocytopenia). In contrast, those who did not respond well initially to medical therapy had relatively poor responses to splenectomy and require continuing medical management.

- The risk of infection is increased after splenectomy, particularly in young child. Therefore, the procedure should be postponed, if possible, until the child is at least 5 years of age. Administration of pneumococcal, meningococcal, and *Hemophilusinfluenzae type b* vaccines prior to splenectomy is recommended. Prophylactic penicillin following splenectomy should be considered.

Prognosis

- 90% of children with ITP will have a spontaneous remission.
- Features associated with the development of chronic ITP include:
  - Female sex
  - Age over 10 years at presentation
  - A more insidious onset of bruising
  - Presence of other autoantibodies

Prognosis

- Severe bleeding is rare (<3% of cases).
- In 70–80% of children with acute ITP, spontaneous resolution occurs within 6 months.
- Therapy does not affect the natural history of the illness.
- Intracranial hemorrhage occurs in less than 1% of patients.
- About 20% of children who present with acute ITP develop chronic ITP.

THROMBOCYTOPENIA WITH ABSENT RADIUS (TAR) SYNDROME

CASE

A 6-month-old infant presents with generalized petechiae. His platelet count is 20,000/mm^3.On X-ray, there are absent radii.

- TARsyndrome is a condition in which thrombocytopenia is associated with bilateral radial aplasia.

Clinical findings

- Episodes of thrombocytopenia begin in the neonatal period in patients with Thrombocytopenia-Absent Radius (TAR) syndrome.
- Symptomatic cow's-milk allergy is associated with 47% of all cases of TAR syndrome, and patients may present as vomiting, bloody diarrhea, and failure to thrive.
- Upper-extremity abnormalities range from isolated absent radii to phocomelia.
- Cardiac anomalies occur in 15–33% of patients and include tetralogy of Fallot, atrial septal defect, or Ventricular Septal Defect (VSD).

Differential diagnosis

- Only patients with TAR syndrome consistently have bilateral absence of the radii with the presence of thumbs and four digits.
- Patients with TAR syndrome always have thumbs, but thumbs may be hypoplastic or absent in patients with **Fanconianemia**.
- Thumb abnormalities include absent, hypoplastic, and triphalangeal thumbs in Holt-Oram syndrome but blood counts are normal.
- Thalidomide embryopathy.
- Trisomy 18 (Edward syndrome).
- VACTERL association.

Diagnosis

- The platelet count may be 15,000–30,000/mm^3.
- Eosinophilia is observed in 50% of patients.
- Leukocytosis may be present.
- Anemia may be present secondary to bleeding.
- Chromosomes are normal. Findings on chromosomal breakage studies with clastogenic agents are normal.
- Characteristic skeletal involvement (i.e. absent radii) is detectable during prenatal transvaginal ultrasonography as early as 13 weeks' gestation.
- After radial aplasia is observed, ultrasonography of the extremities, face, and kidneys is indicated (to detect other anomalies).

Management

- In patients with Thrombocytopenia Absent Radius (TAR) syndrome, general thrombocytopenic precautions include:
  - Avoidance of trauma
  - Avoidance of certain antiplatelet drugs (e.g. aspirin, nonsteroidal anti-inflammatory drugs, and prolonged pressure on injection sites (especially after intramuscular injections).
- The mainstay of treatment is supportive care.
- By far, the most important treatment is platelet transfusion. The goal of platelet transfusion is to maintain a sufficient volume of platelet to prevent bleeding without adverse effects.
- Hematopoietic Stem Cell Transplantation (HSCT) is an option for children who remain thrombocytopenic with bleeding despite platelet transfusions.
- Patients with thrombocytopenia may respond to cytokine treatment with erythropoietin and interleukin-6.

BERNARD-SOULIER SYNDROME

- Bernard-Soulier syndrome is one of a group of hereditary (autosomal recessive) platelet function disorders characterized by:
    - Thrombocytopenia
    - Giant platelets
    - Prolonged bleeding time (tendency toward bleeding)

Clinical findings

- Clinical findings of disorder are usually first noticed at birth and continue throughout life.
- Symptoms of Bernard-Soulier syndrome may include the following:
    - Easy bruising
    - Nosebleeds (epistaxis)
    - Mucosal bleeding
    - Menorrhagia
    - Gastrointestinal bleeding
    - Abnormal bleeding after circumcision or surgery
- Physical findings may include the following:
    - Increased bruising
    - Mucosal bleeding

Differential diagnosis

- Hemophilia
- Thrombasthenia of Glanzmann
- Von Willebrand Disease
- Wiskott-Aldrich syndrome
- Thrombocytopenia with absent radius syndrome

Diagnosis

- Complete Blood Count (CBC), including peripheral smear (showing giant platelets). There are also irregularly shaped platelets.
- Bleeding time (prolonged)
- Platelet aggregation studies:
    - Platelets do not aggregate in response to ristocetin but do have normal aggregation in response to adenosine diphosphate, epinephrine, and collagen.
- Flow cytometry

Management

- Treatment of Bernard-Soulier syndrome is generally supportive.
- In most cases, no medications are needed.
- Bleeding episodes may require specific treatment.
- Antiplatelet medications should be avoided.
- Antifibrinolytic agents (tranexamic acid) may be useful for mucosal bleeding.
- Platelet transfusion is the only available therapy for surgery or potentially life-threatening hemorrhage.
- Desmopressin acetate (DDAVP) shortens the bleeding time in some, but not all, Bernard-Soulier syndrome patients and may be useful for minor bleeding episodes
- Recombinant activated factor VII may be considered.
- Hormonal contraceptives (to control excessive menstrual bleeding).
- For patients with moderate-to-severe symptoms, some restriction of activity may be necessary.

GLANZMANN THROMBASTHENIA

- Glanzmannthrombasthenia is a genetic platelet disorder in which the platelets have qualitative or quantitative deficiencies of the fibrinogen receptor αIIbβ3.
- Glanzmannthrombasthenia is an autosomal recessive disorder.

Clinical findings

- Signs and symptoms include the following:
    - Mucosal bleeding
    - Gingival bleeding
    - Petechiae and ecchymoses
    - Menorrhagia
    - Gastrointestinal bleeding

Diagnosis

- Complete blood cell count
- A normal number of platelets but have a prolonged bleeding time
- Prothrombin time
- Activated partial thromboplastin time
- Flow cytometry
- Monoclonal antibodies confirm the diagnosis

Management

- Treatment includes:
    - Preventive measures such as avoidance of antiplatelet agents (e.g. aspirin and NSAIDs)
    - Iron or folate supplementation for anemia
    - Vaccination for hepatitis B due to the infectious risks associated with multiple transfusions
- Patients who are bleeding require platelet transfusion.
- Recombinant coagulation factor VIIa for bleeding episodes and perioperative management in patients refractory to platelet transfusions, with or without antibodies to platelets.

BLOOD TRANSFUSION

- Whole blood is fractioned into packed red cells, platelets, and fresh frozen plasma or cryoprecipitate.
- Before blood components are given to a patient, donor blood should be screened for hepatitis B, hepatitis C and HIV.
- Both the donated blood and the recipient blood are tested for ABO and Rh(D) antigens.
- Cross-match is needed on any component that contains red blood cells.

- Transfusion components should not be mixed with calcium containing solutions.
- Blood components should not be warmed to temperature more than 37°C.
- If blood bag is pricked, it should be transfused within 4 hours or discarded after 4 hours.
- Packed red blood cells or whole blood should be transfused within 4 hours. Remaining blood is immediately stored in blood bank.
- Before blood transfusion, the unit and the recipient name should be identified carefully.
- Patient should be observed during the entire blood transfusion especially during the initial 15 minutes to evaluate for any blood reaction.
- A test dose of blood transfusion (10% of the total blood given) should be transfused in 15 minutes and then blood transfusion is stopped to evaluate for any reactions. If no blood reaction is observed, the remaining blood is given.

Whole blood transfusion

- Whole blood contains red blood cells and many other plasma components. During storage leukocytes and platelets lose activity after a few days.
- Each unit contains volume of 500 ml.
- Whole blood is indicated in anemia, and blood loss in severe shock.
- It is given as rapidly as tolerated in a case of acute blood loss. In other cases 20 ml/kg is given in 2–4 hours.

Packed red cells transfusion

- Packed red cells contain red blood cells, leukocytes, platelets, and clotting factors. Only plasma is removed.
- It is indicated in chronic anemia, acute trauma or bleeding.
- It is given 3–10 ml/kg as needed in 2–4 hours.
- 3 ml/kg packed red cells will raise the hematocrit by 3%.

Fresh frozen plasma

- This is plasma from whole blood stored at under–18C for up to 1 year.
- It contains >80% of all pro-coagulants and anti-coagulant proteins.
- It is used for replacement of plasma pro-coagulant and anti-coagulant plasma proteins.
- It is given as rapidly as needed in 4 hours. It increases level of all clotting factors by 10–20% if given at a dose of 10–15 ml/kg.

Cryoprecipitate

- It contains factor VIII, fibrinogen, and factor XIII.
- It is used for the treatment of factor VIII, von Willebrand factor, and fibrinogen deficiencies.
- It is given as a rapid infusion. Half pack/kg will increase factor VIII level by 80–100%.

Platelet transfusion

- Each unit contains about 5×10^{10} platelets.
- Platelets transfusions are used in the treatment of thrombocytopenia or platelet function defects.
- It is given as a rapid transfusion in 4 hours. 10 ml/kg platelets transfusion will increase platelet count about 50,000/µL.

Granulocytes transfusion

- It contains 1×10^{10} granulocytes.
- It is use in severely neutropenic patients with poor bone marrow reserves and severe bacterial or fungal infections not responding to antibiotics. It is also used in patients with neutrophil dysfunction.
- It is given 1 unit daily in 4 hours.

Adverse effects following blood transfusion

- Allergic reactions
- Febrile reactions
- Acute hemolytic transfusion reaction
- Bacterial contamination
- Fluid overload
- Iron overload

Notes

CHAPTER 17

Neoplastic Diseases

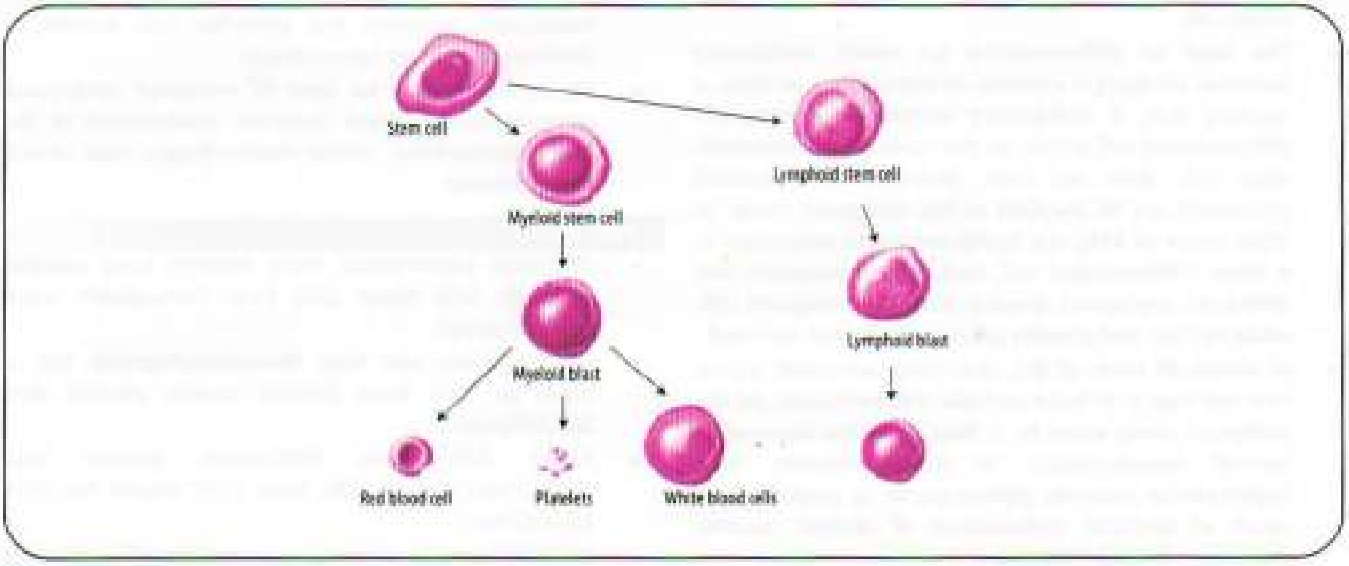


Figure 17.1: Illustration: Origin of blood cells.

LEUKEMIA

CASE

A 7-year-old girl presents with a 3 week history of ***fever***, fatigue, weight loss, limping of left leg and knee pain and listlessness. On examination there are ***petechiae*** and ecchymoses on her abdomen and extremities. There is ***hepatosplenomegaly***. Complete blood count shows a ***white blood cell count*** of 85,000/mm^3 (***raised***), ***hemoglobin*** 7 g/dL (***decreased***) and *platelets* of 15,000/mm^3 (***decreased***). Differential reveals ***80% blasts*** and 20% lymphocytes. Bone marrow examination (blast cells) confirms the diagnosis of acute lymphocytic leukemia.

Definition

- Leukemia is a condition in which there is clonal proliferation of malignant stem cells in the bone marrow.
- Leukemia is present when >25% blast cells are present in bone marrow aspirate.

ACUTE LEUKEMIA

A malignant, clonal proliferation of white cell precursors (blast cells) which occupy and inhibit the function of the bone marrow; they may circulate in the blood and form leukemic deposits in any tissue.

Acute Lymphoblastic Leukemia (ALL)

In ALL (which accounts for 75% of childhood acute leukemias), malignant or blast cells morphologically resemble primitive precursors of lymphoid cells.

Acute Myeloid Leukemia (AML)

- In AML (which accounts for 25% of childhood acute leukemias), malignant or blast cells morphologically resemble myeloid precursors.

Etiology

(Factors predisposing to childhood leukemia)

Genetic conditions

- Down syndrome
- Fanconianemia
- Bloom syndrome
- Diamond-Blackfananemia
- Shwachman-Diamond syndrome
- Kostmann syndrome
- Neurofibromatosis type 1
- Ataxia-telangiectasia
- Severe combined immune deficiency
- Paroxysmal nocturnal hemoglobinuria

Environmental factors

- Ionizing radiation
- Drugs
- Alkylating agents
- Benzene exposure

Pathophysiology

- The precise molecular events or events that cause leukemic transformation are unknown.
- However, there is relentless proliferation of immature hematopoietic cells that have lost their capacity to differentiate normally.
- The development of the leukemia may be a multi-step process, as demonstrated by the fact that in many cases acute leukemia may develop in patients with a pre-existing myelo-dysplastic disorder. The disease is monoclonal, i.e. the final leukemic event occurs in a single cell.
- The level of differentiation (at which malignancy becomes evident) is variable. In some cases of AML, it appears that if malignancy occurs in a very un-differentiated cell similar to the normal hematopoietic stem cell, then red cells, platelets, and myeloid precursors are all involved in the malignant clone. In other cases of AML, the malignant event may occur in a more differentiated cell, and only granulocyte and monocyte precursors develop from the malignant cell, while red cell and platelet precursors are not involved.
- In almost all cases of ALL, the malignant event occurs in a cell that is at least partially differentiated. As the malignant clone expands, it does so at the expense of normal hematopoiesis. In many patients, with hypercellular marrow, pancytopenia is probably the result of physical replacement of normal marrow precursors by leukemic cells.

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

- ALL has a peak incidence at 2–3 years of age.
- It occurs more in boys than in girls at all ages.
- ALL is more common in children with certain chromosomal abnormalities (Down syndrome, Bloom syndrome, ataxia-telangiectasia, and Fanconianemia).

Etiology

- In virtually all cases, the etiology of ALL is unknown.
- Several genetic and environmental factors are associated with childhood leukemia.
- Exposure to medical diagnostic radiation both in utero and in childhood is associated with an increased risk and incidence of ALL.

Clinical findings

- The initial presentation of ALL usually is nonspecific.
- There is anorexia, fatigue, malaise, irritability and an intermittent, low-grade fever.
- Bone or joint pain and swelling may be present. Bone pain is severe and can wake the patient at night.
- As the disease progresses, signs and symptoms of bone marrow failure (pallor, fatigue, exercise intolerance, bruising, or epistaxis, as well as fever, which may be caused by infection or the disease) become more obvious.
- Organ infiltration can cause:
    - ○ Lymphadenopathy
    - ○ Hepatosplenomegaly
    - ○ Testicular enlargement
    - ○ Central Nervous System (CNS) involvement (cranial neuropathies, headache, seizures).
- Respiratory distress is common and may be due to severe anemia or mediastinal lymph node compression of the airways. A large anterior mediastinal mass (e.g. in the thymus or nodes) is most typically seen in adolescent boys with T-cell ALL (T-ALL).
- On physical examination, there may bepallor, listlessness, purpuric and petechial skin lesions, or mucous membrane hemorrhage.
- Rarely, there may be signs of increased intracranial pressure that indicate leukemic involvement of the CNS (papilledema, retinal hemorrhages, and cranial nerve palsies).

Diagnosis

- On initial examination, most patients have **anemia**, although only about 25% have hemoglobin levels below 6 gm/dl.
- Most patients also have **thrombocytopenia**, but as many as 25% have platelet counts greater than 100,000/mm^3.
- About 20% have **WBCcounts** greater than 50,000/mm^3; about 50% have WBC counts less than 10,000/mm^3.
- The diagnosis of leukemia is suggested by the **presence of blast cells on a peripheral blood smear** but is confirmed by **examination of bone marrow**, which is usually completely replaced by leukemic lymphoblasts. If the marrow cannot be aspirated or the specimen is hypocellular, trephine bone marrow biopsy is required.
- **Bone marrow aspiration and biopsy** is a diagnostic test. Normal bone marrow contains less than 5% blast cells. In ALL, there are more than 25% lymphoblasts.
- A **chest radiograph** is necessary to determine whether there is a mediastinal mass or tracheal compression secondary to lymphadenopathy.
- **CSF** should be examined for leukemic cells. CNS leukemia is defined as a CSF white cell count >5/ml with blasts apparent on cyto-centrifuged specimen.

Differential diagnosis

- The diagnosis of leukemia is made in the patient with typical signs and symptoms, anemia, thrombocytopenia, and elevated white blood count with blasts present on smear.
- Elevation of the lactate dehydrogenase is also a clue to the diagnosis of ALL.
- **Aplastic anemia:** presents with anemia, infections and bleeding. There is no lymphadenopathy or hepatosplenomegaly. There is pancytopenia in peripheral blood and bone marrow is hypocellular with decreased number of blast cells.

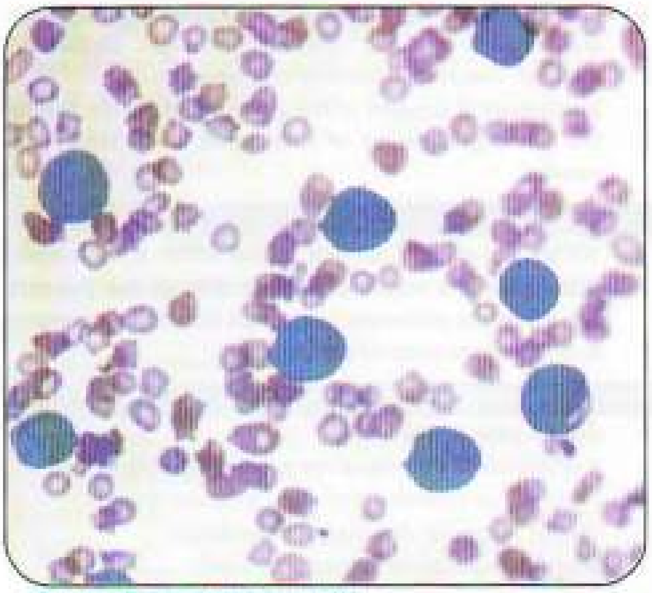


Figure 17.3: Peripheral blood picture in ALL.

- **Myelodysplasia or hypocellularleukemia**
- **Leukemoid reaction** to infections (such as tuberculosis, pertussis).
- **Infectious mononucleosis.** A high index of suspicion is needed to differentiate ALL from infectious mononucleosis in patients with acute onset of fever and lymphadenopathy.
- **Juvenile idiopathic arthritis** in patients with fever, bone pain but often no tenderness, and joint swelling.
- **Idiopathic thrombocytopenic purpura.**
- **Lymphoma:**Tumors of lymphatic system presenting with massive lymphadenopathy. Invasion into peripheral blood is not present and lymph node biopsy is diagnostic.
- ALL must be differentiated from AML and **other malignant diseases that invade the bone marrow** and can have clinical and laboratory findings similar to ALL (including neuroblastoma, rhabdomyosarcoma, Ewing sarcoma, and retinoblastoma).
- **Local infections** e.g. tonsillitis, tooth abscess and sinusitis can lead to regional lymphadenopathy.

Management

- Without effective treatment, the disease is fatal.
- Survival is related to age and subtypes of leukemia.
- Risk-directed therapy has become the standard of current ALL treatment.
    - Age between 1 and 10 years and a leukocyte count of <50,000/μL are used to define standard risk
    - Children who are younger than 1 or older than 10 years of age or who have an initial leukocyte count of >50,000/μL are at high risk
    - Additional characteristics that adversely affect outcome include T-cell immunophenotype or a slow response to initial therapy
    - Chromosomal abnormalities, including hypodiploidy and Philadelphia chromosome have a poorer outcome
- More favorable factors include a rapid response to therapy, hyperdiploidy, and trisomy of specific chromosomes (4, 10, and 17).

Remission induction phase

- Initial therapy is termed as remission induction and is used to eradicate the leukemic cells from the bone marrow.
- During this phase, treatment is given for 4 weeks and consists of:
    - Vincristine weekly
    - A corticosteroid (dexamethasone or prednisone)
    - A single dose of a long-acting, pegylatedasparaginase preparation
    - Patients at higher risk also receive daunomycin at weekly intervals
- With this treatment, 98% of patients are in remission.
- Remission isdefined as <5% blasts in the marrow and a return of neutrophil and platelet counts to near normal levels after 4–5 weeks of treatment.
- Intrathecal chemotherapy is always given at the start of treatment and at least once more time during induction.

Consolidation phase

- The second phase of treatment is called consolidation phase.
- It focuses on intensive **CNS therapy** in combination with continued **intensive systemic therapy**.
- This is aimed as an effort to prevent later CNS relapses.
- Intrathecal chemotherapy is given repeatedly by lumbar puncture.
- By this treatment likelihood of later CNS relapse is reduced to <5%.
- Patient at a high risk of CNS relapse may receive irradiation to the brain in later phases of therapy. These high risk patients include who, at the time of diagnosis, have lymphoblasts in the CSF and either an elevated CSF leukocyte count or physical signs of CNS leukemia (such as cranial nerve palsy).

Intensification phase

- Intensification phase includes phases of aggressive treatment (delayed intensification) as well as relatively nontoxic phases of treatment (interim maintenance).
- Multiagent chemotherapy is used during these phases to eradicate residual disease. These include:
    - Cytarabine
    - Methotrexate
    - Asparaginase
    - Vincristine

Maintenance phase

- This is the final phase of therapy, which lasts for 2–3 years.
- Patients are given daily mercaptopurine and weekly oral methotrexate, usually with intermittent doses of vincristine and a corticosteroid.

Bone marrow transplantation

- Some patients with poor prognostic features (such as those with induction failure or extreme hypodiploidy) may undergo bone marrow transplantation during the first remission.

Treatment of relapse

- The major problem during a successful outcome is relapse of the disease.
- Relapse occurs in the bone marrow in 15–20% of patients with ALL and carries the most serious outcome, especially if it occurs during or shortly after completion of therapy.
- Bone marrow relapse requires:
    - Intensive chemotherapy with agents not previously used in the patient
    - Followed by allogeneic stem cell transplantation
- CNS relapse requires:
    - Intrathecal medication
    - Cranial or craniospinal irradiation
    - Systemic chemotherapy must also be used, because these patients are at high risk for subsequent bone marrow relapse
- Testicular relapse occurs in less than 2% of boys with ALL. This usually occurs after completion of therapy. There is painless swelling of one or both testes. The diagnosis can be confirmed by biopsy of the affected testis. Treatment includes:
    - Systemic chemotherapy
    - Local irradiation

Supportive treatment

- Blood transfusion (Packed RBCs) for anemia, platelet concentrates for thrombocytopenia and granulocyte concentrates for neutropenia.
- Antibiotics are needed for control of infections. Co-trimoxazole is recommended as a prophylaxis against Pneumocystis carinii (*Pneumocystis jiroveci*) pneumonia.
- Allopurinol (10 mg/kg/day in tid for 10 days) is given along with induction therapy to guard against development of uric acid nephropathy as a result of lysis of leukemic cells (tumorlysis syndrome). Alkalinization of urine with IV sodium bicarbonate (1–3 mmol/kg/d) is needed.
- Analgesics are prescribed as required.
- Adequate fluids (3L/m^2/day) and nutritional support should be provided.
- Prophylaxis for malaria is recommended.
- Live virus vaccines are contraindicated. Contact with patients of measles, chicken pox, etc. should be avoided. Hepatitis B vaccine may be given.
- Psychological support of the patient and family, during the prolonged period of illness and its treatment, is needed.

Prognosis

- Without treatment, disease is fatal within a few weeks.
- With adequate treatment about 90% of the patients can achieve a prolonged remission (more than 5 years) and can be considered cured.

Factors responsible for poor prognosis

- Age <1 year or >10 years
- A white blood cell count more than 100,000/m^3
- Presence of a mediastinal mass on chest X-ray
- CNS or testicular disease at presentation
- Massive hepatosplenomegaly (>3 cm)
- Adenopathy present
- Male patient
- T or B–cell disease
- L2 or L3 morphology
- Deletions, translocations and hypodiploidy
- No remission in 4 weeks
- Presence of Philadelphia chromosome in ALL
- LDH high

Factors responsible for good prognosis

- Age between 1 and 10 years
- A white blood cell count under 100,000/mm^3
- Lack of evidence of mediastinal mass
- No CNS or testicular disease at diagnosis
- L1 morphology
- Common ALL
- Female patient
- Hyperdiploidy on chromosomal analysis
- Adenopathy absent
- Hepatosplenomegaly absent to mild (<3 cm)
- LDH not high
- Non-T, Non-B cell ALL
- Rapid response to induction therapy

Tumor lysis syndrome

- Tumor lysis syndrome is a constellation of metabolic disturbances. It may follow the initiation of cancer treatment.
- It usually occurs in patients with large and rapidly proliferating tumors.
- It is more common in acute leukemias and high-grade non-Hodgkin lymphomas.
- Tumor lysis syndrome occurs when large numbers of neoplastic cells are killed rapidly, leading to the release of intracellular ions and metabolic by products into the systemic circulation.

- Clinically, the syndrome is characterized by rapid development of:
    - Hyperuricemia
    - Hyperkalemia
    - Hyperphosphatemia
    - Hypocalcemia
    - Acute renal failure
- Clinically significant tumorlysis syndrome is most often seen 48–72 hours after initiation of cancer treatment.

Clinical findings

- In tumorlysis syndrome, clinical symptoms may develop prior to the initiation of chemotherapy or, more commonly, within 72 hours after administration of cytotoxic therapy.
- Other symptoms of tumorlysis syndrome include the following:
    - Lethargy
    - Edema
    - Fluid overload
    - Congestive heart failure
    - Cardiac dysrhythmias
    - Syncope
    - Sudden death
- Symptoms depend on the severity of underlying metabolic abnormalities.
- Hyperkalemia can cause paresthesia, weakness, and fatal cardiac arrhythmias.
- Severe hypocalcemia can lead to the following clinical findings:
    - Paresthesia and tetany with positive Chvostek and Trousseau signs.
    - Anxiety
    - Carpal and pedal spasms
    - Bronchospasm
    - Seizures
    - Cardiac arrest

Investigations

- Patients at high risk and those with evidence of tumorlysis syndrome should have the following levels monitored at least three times daily:
    - Blood Urea Nitrogen (BUN)
    - Creatinine
    - Uric acid
    - Potassium
    - Calcium
    - Phosphate
    - Lactate Dehydrogenase (LDH)

Management

- The main principles of tumorlysis syndrome management are:
    - Identification of high-risk patients with initiation of preventive therapy.
    - Early recognition of metabolic and renal complications.
    - Prompt administration of supportive care, including hemodialysis.
- Hyperuricemia is controlled with allopurinol.
- Hydration:
    - Volume depletion is a major risk factor for tumorlysis syndrome. It must be corrected vigorously.
    - Aggressive IV hydration helps to correct electrolyte disturbances by diluting extracellular fluid.
    - Increased volume enhances renal blood flow, glomerular filtration rate, and urine volume to decrease the concentration of solutes in the distal nephron and medullary microcirculation.
    - IV hydration in high-risk patients should begin 24–48 hours before initiation of cancer therapy and continue for 48–72 hours after completion of chemotherapy.
    - Continuous infusion rates as high as 3 L/m^2 daily should be given.
- Urinary alkalinization:
    - The use of isotonic sodium bicarbonate solutions intravenously to promote alkaline diuresis has the benefit of solubilizing, and thus minimizing, intratubular precipitation of uric acid.
- Treatment of hyperkalemia:
    - Aggressively treat and monitor hyperkalemia.
    - Immediately restrict dietary potassium and remove potassium from IV fluids.
    - Acute treatment modalities include IV infusion of glucose plus insulin to promote redistribution of potassium from the extracellular to the intracellular space, and IV calcium gluconate as cardioprotection for potassium levels greater than 6.5 mmol/L or for patients with electrocardiographic changes.
- Treatment of hyperphosphatemia and hypocalcemia:
    - Hyperphosphatemia is managed with oral phosphate binders and the same solution of glucose plus insulin used for the control of hyperkalemia. Hyperphosphatemia may lead to hypocalcemia, which usually resolves as phosphate levels are corrected.
- Dialysis:
    - If the above treatments for the complications of tumorlysis syndrome fail, consider early initiation of dialysis.
    - Dialysis prevents irreversible renal failure and other life-threatening complications.
    - Indications for dialysis include persistent hyperkalemia or hyperphosphatemia despite treatment, volume overload, uremia, symptomatic hypocalcemia, and hyperuricemia.

Prognosis

- Early recognition of signs and symptoms of patients at risk for tumorlysis syndrome can lead to successful prevention of the otherwise life-threatening complications of the condition.
- Severe electrolyte disturbances, such as hyperkalemia and hypocalcemia, predispose patients to cardiac arrhythmia and seizures.

ACUTE MYELOGENOUS LEUKEMIA (AML)

- The relative frequency of AML increases in adolescence.
- Several chromosomal abnormalities associated with AML have been identified, but no predisposing genetic or environmental factors can be identified in most patients.
- The characteristic feature of AML is that >20% of bone marrow cells on bone marrow aspiration or biopsy are blast cells, with features similar to those that characterize early differentiation states of the myeloidmonocyte-megakaryocyte series of blood cells.

Clinical findings

- Symptoms and signs of AML is a result of replacement of bone marrow by malignant cells and bone marrow failure.
- There are any or all of the findings associated with marrow failure in ALL.
- In addition, patients with AML present with subcutaneous nodules (blueberry muffin lesions especially in infants), infiltration of the gingiva (especially in monocytic subtypes), signs and laboratory findings of disseminated intravascular coagulation, and discrete masses, known as chloromas or granulocytic sarcomas.

Diagnosis

- Analysis of bone marrow aspiration and biopsy specimens:
    - Show the features of a hypercellular marrow consisting of a monotonous pattern of cells
- Flow cytometry and special stains:
    - Show myeloperoxidase-containing cells (confirming myelogenous origin of the leukemia and the diagnosis)
- Specific subtypes of AML are diagnosed by *chromosomal abnormalities and molecular genetic markers.*

Management

- Aggressive multiagent chemotherapy is required for AML.
- It is successful in inducing remission in approximately 85–90% of patients.
- Infections and bleeding are main complications and up to 5% of patients die of either infection or bleeding before remission.
- Matched-sibling bone marrow or stem cell transplantation after remission increases survival.
- Matched unrelated donor bone marrow transplants are usually reserved for patients who have a relapse.
- Increased supportive care is required in patients with AML, especially *streptococcal viridans*sepsis and fungal infection. These patients may require prolonged hospitalization, granulocyte colony stimulating factor, and prophylactic antimicrobials.

LYMPHOMAS

CASE

A 10-year-old girl presents with a two-month history of a painless right-sided neck swelling (***lymphadenopathy***). There is history of increasing cough over the previous 2 weeks (***dyspnea***) and ***dysphagea***. She also has ***fever***, especially at night, and ***weight loss***. On examination she had bilateral supraclavicular lymphadenopathy, more marked on the right side. She had axillary and inguinal lymphadenopathy and ***splenomegaly***. A chest radiograph showed hilarlymphadenopathy, and a ***large mass in the mediastinum***.

- Malignant lymphomas are the third most common tumor in the childhood (after leukemia and brain tumors).
- Lymphomas are broadly categorized into Hodgkin disease and non-Hodgkin lymphoma.

HODGKIN LYMPHOMA (HL)

- It is characterized by the presence of B-cell derived Reed-Sternberg cells.
- Hodgkin lymphoma in children behaves similarly to the disease in adults. It is a malignant process involving the lymphoreticular system.
- Hodgkin lymphoma accounts for 6% of all childhood cancer.
- It occurs in older children and has a slight female predominance.
- Infectious agents may be a cause, such as:
    - Human herpesvirus 6.
    - Cytomegalovirus.
    - Epstein-Barr Virus (EBV). Infection with EBV is related to four fold higher risk of developing HL.

Pathogenesis

- **Reed-Sternberg (RS) cell** is a pathognomonic feature of HL. It is a large cell with multiple or multilobulated cells. It is also seen in infectious mononucleosis, NHL, and other conditions.
- HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils in different proportions.

The interaction between the RS cell and these background inflammatory cells with their associated cytokine release is main pathology in the development and progression of HL.

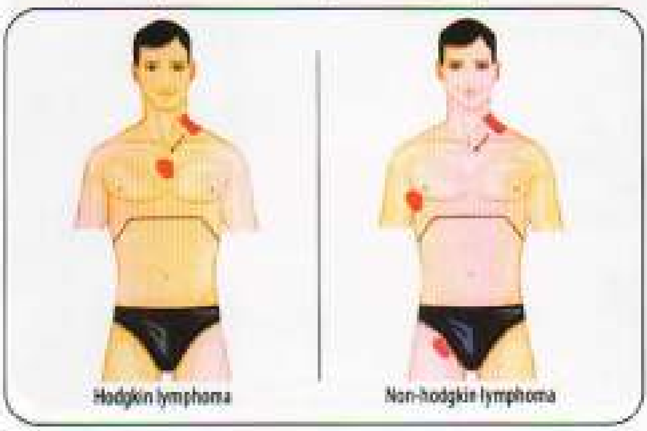


Figure 17.3: Typical involvement of lymph nodes in lymphoma.

Clinical findings

- Painless, firm localized lymphadenopathy, especially in the cervical region, is the most common presenting symptom.
- There is usually some degree of mediastinal involvement.
- Clinically detectable hepatosplenomegaly is rare.
- Systemic (B) symptoms occur in up to 30% of children and consist of:
  - Temperature exceeding 38°C (100.4°F)
  - Drenching night sweats
  - Weight loss in excess of 10% of body weight in 6 months
- Symptoms and signs depend on the extent and location of nodal and extranodal disease.
- Patients may present with symptoms and signs of airway obstruction (dyspnea, hypoxia, and cough), pleural or pericardial effusion, hepatocellular dysfunction, or bone marrow infiltration (anemia, neutropenia, or thrombocytopenia).
- Disease manifestations below the diaphragm are rare (approximately 3% of all).

Diagnosis

- Evaluation includes history, physical examination, and imaging studies.
- Complete blood count, platelets count.
- Erythrocyte sedimentation rate and measurement of serum ferritin (which are of some prognostic significance and serves as a baseline to evaluate the effects of treatment).
- Chest X-ray with measurement of mediastinal ratio (measuring the size of the mediastinal mass in relation to the maximal diameter of the thorax). This shows bulk disease and has prognostic significance.
- CT scan neck, chest, and abdomen. Chest CT more clearly defines the extent of a mediastinal mass.
- PET (Positron Emission Tomography) is useful for staging and classification of lymphoma.
- Excisional biopsy of lymph nodes.
- The diagnosis depends on the identification of Reed-Sternberg cells in tumor tissue.
- Bone marrow aspiration and biopsy should be performed to rule out advanced disease. Bone marrow examination is performed in advanced disease (stage III, IV or 'B' symptoms).
- Liver Function Tests (LFTs).
- Renal parameters.
- Lactate Dehydrogenase (LDH).

Management

- Treatment is determined largely by disease stage, presence or absence of B symptoms, and the presence of bulky nodal disease.

Combination chemotherapy

- Multi-agent chemotherapy is now the cornerstone of treatment.
- It is supplemented, in selected cases by relatively low dose radiation.
- The majority of children are treated with:
  - ABVD (Adriamycin, Bleomycin, Vincristine, and Dacarbazine).
  - COPP(Cyclophosphamide, Vincristine [Oncovin], Procarbazine, and Prednisone).
  - BAVD(BrentuximabVedotin, Doxorubicin [Adriamycin], Vincristine, dacarbazine).
  - Multiple agents have different mechanisms of action. They have non-overlapping toxicities so that full doses can be given to each patient.

Radiotherapy

- Radiotherapy to involved nodes plus the next node group to which spread could occur is often used for localized disease.
- For patients treated with radiotherapy alone, chemotherapy can sometimes be used as successful therapy for relapse.

Prognosis

- Prognosis is good and varies from 90% cure of stage I disease to a 50% cure of stage IV disease.
- Late effects of above treatment are secondary malignancies, thyroid gland dysfunction, and growth disturbances after irradiation and sterility.

NON-HODGKIN LYMPHOMA (NHL)

- NHL is a heterogeneous group of diseases characterized by neoplastic proliferation of immature lymphoid cells, which, unlike the malignant lymphoid cells of ALL, accumulate primarily outside the bone marrow.
- NHL comprises 6% of all childhood cancers.
- Non-Hodgkin Lymphoma (NHL) accounts for approximately 60% of lymphomas in children.

- They occur predominantly in older children and have a strong predilection for males.
- Childhood NHL differ from many adult cases in that they are:
  - Predominantly extra-nodal in presentation
  - Are likely to be T–cell lymphomas
  - Highly aggressive
  - Rarely of nodular histology
- **Burkitt lymphoma** presents as a mass in the jaw or abdomen. It has been linked to a prior Epstein-Barr virus infection occurring in a young child who has been immuno-suppressed by malaria or another infection.

Clinical findings

- All childhood non-Hodgkin lymphomas are rapidly growing and thus, duration of symptoms is short.
- **Anterior mediastinal masses**, sometimes associated with pleural effusions, are the most common presentation of T-cell, or lymphoblastic lymphomas. They can produce respiratory distress from airway compromise and superior vena cava syndrome.
- **Abdominal masses** are the most common presentation of B-cell, or non-lymphoblastic lymphomas. They can cause abdominal enlargement from a rapidly growing tumor, sometimes producing pain, ascites, and urinary tract or intestinal obstruction.
- **Painless peripheral lymph node enlargement** can be seen with any type of childhood non-Hodgkin lymphoma. Less common presentations include obstructing nasopharyngeal tumor, bone tumor or skin tumor.

Staging

- Various systems are employed for different types of childhood non-Hodgkin lymphoma. They all distinguish:
  - **Local disease** of limited bulk often confined to one side of the diaphragm and carrying a good prognosis.
  - **Extensive disease** within the mediastinum or abdomen.
  - **Hematogenous dissemination**, especially to the bone marrow and meninges.

Diagnosis

- Complete blood count with platelet count
- Serum electrolytes, uric acid and Lactate Dehydrogenase (LDH)
- Renal parameters
- Chest X-ray and CT scan chest
- Neck, chest, abdominal, and pelvic CT scans (head CT for suspicion of CNS disease), and PET scan.
- Abdominal and pelvic ultrasonography
- Bone scan
- Bone marrow aspiration and biopsy
- CSF cytology
- The diagnosis is established by tissue biopsy

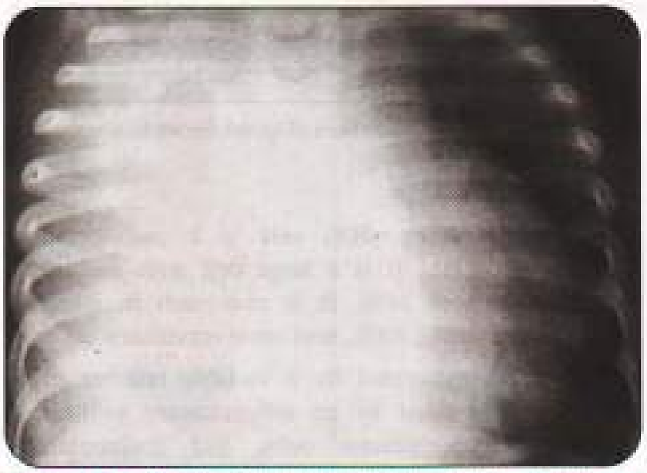


Figure 17.4: X-ray chest: Right-sided pleural effusion in lymphoma.

Management

- Lymphoblastic NHL is treated as that of acute lymphoblastic leukemia.
- **Systemic chemotherapy** is needed in all cases to shrink the local tumor and to prevent dissemination to the bone marrow or to a leukemic phase. The intensity and duration of therapy depends on the type of lymphoma and on the stage of the disease.
- **CNS prophylaxis** in some form is required in most patients.
- **Radiotherapy** is indicated in treatment sites where there is life-threatening obstruction (trachea, bronchi, or superior vena cava) that does not respond to chemotherapy, or a bulk tumor for which chemotherapy alone is inadequate.

Complications

- Complications of multi-agent chemotherapy:
  - Serious mucositis
  - Infections
  - Cytopenias that require red blood cell and platelet blood product transfusions
  - Electrolyte imbalances
  - Poor nutrition
- Long-term complications:
  - Growth retardation
  - Cardiac toxicity
  - Gonadal toxicity with infertility
  - Secondary malignancies

Prognosis

- With appropriate management of the metabolic consequences of rapid cell turnover and with the institution of therapy, prognosis is excellent.
- Without therapy, rapid and wide-spread dissemination occurs.
  - T–cell lymphomas spread to the bone marrow and meninges and then closely resemble T–cell ALL.

    - B–cell lymphomas of Burkitt type spread to the bone marrow and meninges and closely resemble B–cell (L3) ALL.
- Patients with localized disease have a 90–100% chance of survival, and those with advanced disease have a 70–95% chance of survival.

BRAIN TUMORS IN CHILDHOOD

CASE

A 3-year-old girl presents with a recent history of ***ataxia***, ***slurred speech***, and ***early morning vomiting***. There is history of ***headache*** for about a month. On examination, she has brisk stretch reflexes in all four extremities, bilateral extensor plantar response (Babinski reflex) and mild hypertonicity of the left upper and lower extremities. There is no muscular weakness. CT scan brain shows a 4 cm lesion in her posterior fossa occluding the fourth ventricle and causing obstructive hydrocephalus.

- Brain tumors are the second most common form of childhood cancer (20% of the total).

Classification

Location

- Two third of brain tumors arise below the tentorium (infratentorialtumors).
- One third arises above the tentorium (supratentorealtumors).

Histology

- High-grade astrocytomas
- Arise primarily above the tentorium
- Presents as focal neurologic deficits, signs of increased intracranial pressure, and focal seizures

Low-grade astrocytomas:

- Arise primarily below the tentorium in the cerebellum
- It presents as signs of increased intracranial pressure, and signs of cerebellar dysfunction (e.g. ataxia, nystagmus)

Brain stem gliomas:

- Present as multiple cranial nerve palsies, ataxia, and long tract signs

Ependymomas:

- Develop more commonly below the tentorium
- Presents with symptoms of increased intracranial pressure when they obstruct the fourth ventricle

Medulloblastoma:

- It is the most common malignant brain tumor in children.
- Its characteristic presentation is that of a cerebellar tumor.
- There are signs of increased intracranial pressure (headache, vomiting, and lethargy). The tumor often obstructs the fourth ventricle.
- There is cerebellar dysfunction.
- Propensity for rapid spread throughout the neuraxis by the CSF pathways.

Primitive neuro-ectodermal tumors:

- These are highly malignant.

Clinical findings

- Clinical presentation of the brain tumor depends on the tumor location, the tumor type, and the age of the child.
- The evaluation of a patient in whom a brain tumor is suspected causes an emergency.
- Initial evaluation should include a complete history, physical (including ophthalmic) examination, and neurologic assessment.
- If there is obstruction of cerebrospinal fluid (CSF) drainage paths (leading to increased intracranial pressure) or focal brain dysfunction by the tumor, following findings are observed:
    - Subtle changes in personality, mentation, and speech
    - Vomiting, lethargy, and irritability
- The **classic triad** is headache, nausea, and vomiting as well as papilledema.
- It is associated with midline or infratentorialtumors.
- Disorders of equilibrium, gait, coordination, blurred vision, diplopia, and nystagmus also occur with infratentorialtumors.
- Torticollis may occur in cerebellar tonsil herniation.
- Tumors of the brainstem region present with gaze palsy, multiple cranial nerve palsies, and upper motor neuron deficits (e.g. hemiparesis, hyperreflexia, clonus).
- Supratentorialtumors present with lateralized deficits:
    - Focal motor weakness
    - Focal sensory changes
    - Language disorders
    - Focal seizures
    - Reflex asymmetry
- Infants with supratentorialtumors may have premature hand preference.
- Optic pathway tumors present with decreased visual acuity, nystagmus, or visual field defects.
- Supra-sellar region tumors present as neuroendocrine deficits:
    - Subacute development of obesity
    - Abnormal linear growth velocity
    - Diabetes insipidus
    - Galactorrhea
    - Precocious puberty
    - Delayed puberty
    - Hypothyroidism
- Diencephalic syndrome (diencephalic region tumors):
    - Failure to thrive
    - Emaciation despite normal caloric intake

  - Inappropriately normal or happy affect
- Parinaud syndromeis seen with pineal region tumors and presents with:
  - Paresis of upward gaze
  - Pupillary caliber reactive to accommodation but not to light (pseudo-Argyll Robertson pupil)
  - Nystagmus to convergence or retraction, and eyelid retraction
- Spinal cord tumors present as long nerve tract deficits often localized to below a specific spinal level, bowel and bladder deficits, and back pain.

Diagnosis

- **MRI** is the neuroimaging standard. Tumors in the pituitary or suprasellar region, optic path, and infratentorium are better detected with MRI than with CT.
- Patients with tumors of the midline and the pituitary or suprasellar or optic chiasmal region should be evaluated with neuroendocrine studies.
- The suprasellar and pineal regions are sites for germ cell tumors. Serum and CSF measurements of β-human chorionic gonadotropin and α-fetoprotein can help to diagnose the germ cell tumors.
- Lumbar puncture for cytologic analysis of the CSF is indicated to diagnose some tumors but lumbar puncture is contraindicated in individuals with hydrocephalus secondary to CSF flow obstruction, in tumors that cause supratentorial midline shift, and in individuals with infratentorialtumors. Lumbar puncture in these individuals may lead to brain herniation, resulting in neurologic compromise and death.

Management

Special problems in management

- The blood-brain barrier limits the absorption of chemotherapy by the systemic route.
- The developing brain of infants and young children is vulnerable to the toxicity of radiotherapy and chemotherapy.
- Some tumors are near the important areas of the brain, which does not allow the extensive surgical resection.
- Tumors spread within the neuraxis.

Surgery

- Respectable tumors include cerebellar and cerebral tumors.
- Brain-stem gliomas usually are not respectable.

Radiotherapy

- It has a major role in the management of tumors in all locations.
- It is indicated for most tumors except completely resected low-grade astrocytomas.
- Toxic effects are learning dis-abilities, and growth failure.
- Whole neuraxis (cranium and spine) must be irradiated for tumors (e.g. medulloblastoma) that spread throughout the neuraxis.

Chemotherapy

- Prolongs the survival of patients with high-grade astrocytomas.
- Increase the cure rate in medulloblastoma.
- Controls the tumor growth in infants and young children, so that radiotherapy can be postponed to somewhat later age (when radiotherapy is less toxic to developing brain).

Prognosis

- Prognosis is excellent for completely resected low-grade cerebellar astrocytomas.
- Prognosis is good for medulloblastoma especially if they occur in children older than 4 years of age, are relatively small in size, and have not spread.
- Prognosis is poor for brain-stem gliomas.

NEUROBLASTOMA

CASE

A 3-year-old girl presents with decreased energy, loss of appetite, and an enlarging abdomen over the past few weeks. Now, there is intermittent emesis. Physical examination reveals ***pallor***, bilateral ***proptosis***, ***periorbital discoloration*** (ecchymoses), and a large, irregular ***abdominal mass*** along her left flank that crosses the midline (muti-quadrant abdominal mass). On investigations, there is pancytopenia.

- Neuroblastoma is a malignancy of neural crest cells.
- It arises in para-spinal sympathetic ganglia and the adrenal medulla.
- It is the second most common solid tumor of childhood (incidence 7%). Only brain tumors are more common.
- Neuroblastoma occurs predominantly in infants and preschool children (<2 years).

Clinical findings

- About one half of newly diagnosed patients with neuroblastoma have distant metastases at diagnosis and they appear ill.

Abdominal tumors

- This is the most common presentation.
- Half arise from extra-adrenal tissue and half from the adrenal medulla.
- Presenting features are abdominal mass (often displaces the kidneys antero-laterally and inferiorly), abdominal pain, and systemic hypertension.

Thoracic tumors

- Located in the posterior mediastinum.

- Presenting features are respiratory distress, or incidental finding on a chest radiograph obtained for unrelated symptoms.

Head and neck tumors

- These are palpable tumors that sometimes produce Horner's syndrome (miosis, ptosis, enophthalmos, anhidrosis, and heterochromia of the iris on the affected side).

Epidural tumors

- These arise from the posterior growth of abdominal or thoracic tumors.
- These compress the spinal cord and produce back pain and symptoms of cord compression.

Metastases

- Weight loss, fever
- Bone marrow failure
- Cortical bone pain (limp if present in lower extremity)
- Proptosis and periorbitalecchymoses (retro-bulbar and orbital infiltration)
- Liver infiltration (hepatomegaly)
- Distant lymph node enlargement
- Skin infiltration (palpable sub-cutaneous nodules)

Staging

- Stage I and II: Tumors must not be large enough to cross midline.
- Stage III: Tumors cross the midline.
- Stage IV: Metastatic tumors.
- Stage IVS: In infants metastases limited to the skin, liver, and bone marrow but not cortical bone.

Diagnosis

- Plain radiograph
- CT scan or MRI
- Neuroblastoma is usually present as a mass or multiple masses on plain radiography, CT, or MRI. The mass often contains calcification and hemorrhage.
- Evaluations for metastatic disease should include CT or MRI of the chest and abdomen.
- Tumor markers: catecholamine, VMA (Vanillyl-Mandelic Acid) or HVA (Homo-Vanillic Acid) are elevated in urine in about 95% of cases and are diagnostic.
- Biopsy of the lesion and bone marrow.Neuroblastoma can be diagnosed without a primary tumor biopsy if small round blue tumor cells are observed in bone marrow samples and tumor markers are elevated in urine.
- Bone scan to see bone metastasis.
- Prenatal diagnosis of neuroblastoma on maternal ultrasound scans may be possible.
- Iodine-123 meta-iodo-benzyl-guanidine (123I-MIBG) studies are used to better define the extent of disease.

Management

- Surgery for stage I and II tumors.
- Spontaneous regression without any treatment is common in stage IVS tumors. Only observation is required.
- Aggressive multi-agent chemotherapy in stage III and IV.
- Chemotherapy usually includes moderate doses of cisplatin or carboplatin, cyclophosphamide, etoposide and doxorubicin.
- Autologous bone marrow transplantation for stage III and IV patients who have a poor prognosis.

Prognosis

- Best prognosis in infants younger than 1 year of age.
- Good prognosis for stage I and II patients and stage IVS infants.
- Poor prognosis in stage III and IV patients.
- Poor prognosis if serum markers are elevated.

WILMS TUMOR

CASE

A 4-year-old boy presents with a ***mass in the abdomen***. The mass was painless. Physical examination reveals a resting blood pressure of 130/88 mmHg (***hypertension***), heart rate of 82 beats/minute, pallor, and a firm left-sided abdominal mass that doesn't cross the midline. A thorough medical evaluation of the child reveals ***aniridia***, hypospadias, horseshoe kidney, and ***hemihypertrophy***. Complete urine examination shows ***hematuria***.

- WilmsTumor (WT) or nephroblastoma is the most common primary malignant renal tumor of childhood.
- It is the second most common malignant abdominal tumor in childhood.
- The most common sites of metastases are the lungs, regional lymph nodes, and liver.
- Wilmstumor is 6% of all childhood cancers. It accounts for more than 95% of kidney tumors in children.
- It predominantly occurs during the first 5 years of life. Occurrence is equal in males and females.
- It can arise in one or both kidneys. The incidence of bilateral WT is 7%.
- Most cases are sporadic. But approximately 2% of patients have a family history.
- Wilmstumor may be associated with hemihypertrophy, aniridia, genitourinary anomalies, Beckwith-Wiedemann syndrome and Denys-Drash syndrome.

Clinical findings

Abdominal mass

- Most common presentation.

- Mass is usually asymptomatic and detected on routine physical examination.
- Mass characteristically occurs within the kidney and displaces and distorts the renal collecting system.

Hypertension

- It is related to elaboration of rennin by tumor cells.
- It may be due to compression of the renal vasculature by the tumor.

Hematuria

- Painless
- Gross

Abdominal pain

- It is due to hemorrhage into the tumor.
- It may be associated with fever and anemia.

Genetic factors

- Up to 20% of Wilmstumors are hereditary.

Associated abnormalities

- Aniridia
- Hemihypertrophy

Diagnosis

- Appropriate imaging studies (plain abdominal radiography, ultrasonography or CT of the abdomen) are used to evaluate the site of origin within the kidney and its invagination into inferior vena cava and extension beyond its origin. Contra lateral kidney is also evaluated for tumor.
- Search for distant metastases is undertaken in lungs, liver, bones, and brain.

Differential diagnosis

- Adrenal masses (e.g. neuroblastoma)

Management

Surgery

- Removal of lymph nodes, selected metastases and primary tumor (by nephrectomy except in the case of bilateral tumors where at least part of one kidney must be preserved).

Radiotherapy

- Radiotherapy is done for residual local disease and selected metastatic foci.

Chemotherapy

- Preoperative chemotherapy can make surgery easier. It reduces the risk of intraoperative tumor rupture and hemorrhage.
- Actinomycin D and vincristine are used to treat all stages of disease.
- Additional agents, including cyclophosphamide and doxorubicin, are used to treat patients who have a poor prognosis.

Prognosis

- Patients with localized disease and a favorable histology have a greater than 90% chance of survival.
- Patients who have distant metastases do least well.
- Patients with unfavorable histology often do poorly. They have anaplastic Wilmstumor or sarcomatousWilmstumor.

RETINOBLASTOMA

CASE

A 4-year-old girl presents with a ***white pupil*** on the right. On examination, the right pupil is white, mid-dilated and ***unresponsive to light***. An ocular ultrasound shows that the vitreous cavity is filled with a mass that is highly reflective and solid. Attempts to visualize the fundi are unsuccessful.

- Retinoblastoma is an embryonal malignancy of the retina and the most common intraocular tumor in children.
- Retinoblastoma is a congenital malignancy.
- It arises from neural tissue within the retina.

Clinical findings

- An abnormal white pupil (leukocoria) is usually present.
- It is often first noticed when a red reflex is not present at a routine newborn or well-child examination.
- Strabismus is sometimes present.
- At diagnosis most tumors are localized to the eye.
- Decreased vision, orbital inflammation, hyphema, and pupil irregularity can occur with advancing disease.
- Metastases occur late and spread to the meninges via the optic nerve or bone marrow and cortical bone via the blood.

Diagnosis

- Retinoblastoma is diagnosed by the characteristic ophthalmologic findings.
- Imaging studies are not diagnostic.
- Biopsy is contraindicated.
- Indirect ophthalmoscopy with slit-lamp evaluation can detect retinoblastoma.
- A complete evaluation requires an examination under general anesthesia by an experienced ophthalmologist.
- Orbital ultrasonography, CT, or MRI is used to evaluate the extent of intraocular disease and extraocular spread. MRI allows for better evaluation of optic nerve involvement.

Differential diagnosis

- Other causes of leukocoria:
  - Persistent hyperplastic primary vitreous
  - Coats disease
  - Vitreous hemorrhage

  - Cataract
  - Endophthalmitis from *Toxocaraconis*
  - Choroidalcoloboma
  - Retinopathy of prematurity
  - Familial exudative vitreoretinopathy

Management

- The goal is to cure and preserve useful vision whenever possible.
- Surgical enucleation was indicated for unilateral disease and most severely involved eye in bilateral cases.
- With bilateral disease, chemoreduction in combination with focal therapy (laser photocoagulation or cryotherapy) is indicated now. It has replaced approach of enucleation of the more severely affected eye.
- Radiotherapy is indicated to treat any residual orbital disease.
- Chemotherapy is used as an adjuvant and palliative treatment for disseminated disease. Multi-agent chemotherapy, include carboplatin, vincristine, and etoposide.
- All first degree relatives of children with retinoblastoma should have retinal examinations to identify retinomas or retinal scars, which may suggest hereditary retinoblastoma.

Prognosis

- Prognosis is excellent for those patients whose disease is limited to the eyes.
- Dissemination (retinoblastoma that has spread outside of the eye) is associated with poor prognosis.
- Trilateral retinoblastoma (disease involving both eyes and the pineal region) is almost universally fatal.

BONE TUMORS

CASE

A 10-year-old child presents with severe pain in right thigh for last 1 month. He is limping. On X-ray, there is a lytic lesion in femur.

- Osteosarcoma is the most common primary malignant bone tumor in children, followed by Ewing sarcoma.
- Ewing sarcoma is more common than osteosarcoma in children younger than 10 years of age.

OSTEOSARCOMA

- The highest risk period for development of osteosarcoma is during the growth spurt. There is an association between rapid bone growth and malignant transformation.
- Cause of osteosarcoma is unknown, but certain genetic or acquired conditions predispose patients to development of osteosarcoma.
- Hereditary retinoblastoma, Li-Fraumeni syndrome, Paget disease, radiotherapy are associated with increased risk of osteosarcoma.
- Common site of involvement is metaphyses of long bones.

Clinical findings

- Pain, limp, and swelling are the most common presenting manifestations.
- Other clinical findings may include limitation of motion, joint effusion, tenderness, and warmth.

Diagnosis

- Bone tumor should be suspected in a child who presents with deep bone pain or pain causing night-time awakening or a palpable mass.
- Radiograph of the mass demonstrate a lesion. The lesion may be mixed lytic and blastic in appearance (sunburst pattern). New bone formation is usually visible.
- Biopsy of the tumor
- The metastatic work-up includes CT of the chest and radionuclide bone scanning to evaluate for lung and bone metastases, respectively.

Differential diagnosis

The differential diagnosisof a lytic bone lesion includes:

- Histiocytosis
- Ewing sarcoma
- Lymphoma
- Bone cyst

Management

- Chemotherapy and surgery are main treatments.
- Complete surgical resection of the tumor is important for cure.
- Preoperative chemotherapy is an initial step to facilitate limb salvage operations.
- Limb salvage operations are indicated after initial chemotherapy.
- Chemotherapy is resumed as soon as possible after surgery.
- Lung metastases should also be resected by thoracotomies.
- Multi-drug chemotherapy includes doxorubicin, cisplatin, methotrexate and ifosfamide.
- Histologic response to chemotherapy is one of the most important prognostic factors in osteosarcoma.
- After limb salvage surgery, intensive rehabilitation and physical therapy are necessary. These will ensure maximal functional outcome.
- In case of limb amputation, early prosthetic fitting and gait training are essential for normal activities.

Prognosis

- Surgical resection alone is curative only for patients with parosteal osteosarcoma.

- Up to 75% of patients with nonmetastatic extremity osteosarcoma are cured with current multiagent chemotherapy.
- Prognosis is not as good for patients with pelvic tumors as for those with primary tumors in the extremities.
- Patients with bone metastases and widespread lung metastases have an extremely poor prognosis.
- Late effects of chemotherapy are cardiotoxicity from anthracycline and hearing loss from cisplatin.

EWING SARCOMA

- Ewing sarcoma tumorsarea group of small, round cell, undifferentiated tumors of neural crest origin.
- Anatomic sites of primary tumors are the extremities and the central axis (pelvis, spine, and chest wall).
- Primary tumors arising in the chest wall are called Askintumors.

Clinical findings

- Symptoms of Ewing sarcoma are same as those of osteosarcoma.
- Common presenting symptoms are pain, swelling, limitation of motion, and tenderness over the involved bone or soft tissue.
- Patients with primary chest wall tumors may present with respiratory distress.
- Paraspinal or vertebral primary tumors may present with symptoms of cord compression.
- Systemic manifestations arefever and weight loss.

Diagnosis

- The diagnosis of Ewing sarcoma should be suspected:
  - With pain and swelling
  - With or without systemic symptoms
  - With a radiographic appearance of a primarily lytic bone lesion with periosteal reaction (onion-skinning)
- A large soft tissue mass associated with tumor often is visualized on MRI or CT.
- CT-guided biopsy of the lesion often provides adequate diagnostic tissue.
- A thorough evaluation for metastatic disease includes:
  - CT of the chest
  - Radionuclide bone scan
  - Bone marrow aspiration and biopsy specimens from at least 2 sites
- MRI of the tumor and the entire length of involved bone is indicated. This will determine:
  - The exact extension of the soft tissue and bony mass
  - The proximity of tumor to neurovascular structures
- Fluorodeoxyglucose positron emission tomography scanning is used for staging.

Differential diagnosis

- Osteosarcoma
- Osteomyelitis
- Langerhans cell histiocytosis
- Primary lymphoma of bone
- Metastatic neuroblastoma
- Rhabdomyosarcoma (in the case of a pure soft tissue lesion)

Management

- Ewing sarcoma tumors are best managed with a comprehensive multidisciplinary approach (surgery, chemotherapy, radiation therapy).
- Multiagent chemotherapy can shrink the tumor rapidly. It also causes significant pain relief.
- Ewing sarcoma is a radiosensitive tumor, and local control may be achieved with irradiation or surgery.
- But, radiation therapy may be associated with:
  - A risk of radiation-induced second malignancies, especially osteosarcoma
  - Failure of bone growth in skeletally immature patients

Prognosis

- Patients with small, nonmetastatic, distally located extremity tumors have the best prognosis.
- Pelvic tumors have a much worse outcome.
- Patients with metastatic disease, especially bone or bone marrow metastases, have a poor prognosis.

LANGERHANS CELL HISTIOCYTOSIS

CASE

A 4-year-old girl presents with ***fever***, moderate cervical and axillary ***lymphadenopathy*** and marked ***hepatosplenomegaly***. Blood count shows ***pancytopenia***. Blasts are not identified on the peripheral smear. She has a ***coagulopathy*** with prolongation of PT and APTT, hypofibrinogenemia and raised D-dimers. Triglycerides level is raised. A bone marrow aspirate shows marked hypocellularity with prominent hemophagocytosis. X-ray skull showing ***multiple punched out lesions***.

- The Langerhans cell histiocytosis (histiocytosis X) has a prominent proliferation or accumulation of cells of the monocyte–macrophage system of bone marrow origin.

Clinical findings

LCH presents in an extremely variable way.

The skeleton is involved in about 80% of patients.

- Bone lesions may be single or multiple and commonly are in the skull.
- Bone lesions may be asymptomatic or associated with pain and local swelling.

lymphoma. In such disorders, it is often associated with lymphadenopathy. It is also an important finding in myeloblasticleukemia. In neuroblastoma, there is metastatic involvement of the spleen.

- In hepatic cirrhosis and congestive cardiac failure, there is impaired blood flow in the spleen or portal venous system.
- In storage diseases, there is infiltration of the spleen with abnormal material.
- Extra-medullary hematopoiesis may occur in diseases associated with intense demand on the bone marrow for cell production. Such disorders include thalassemia major and osteopetrosis.
- Hypersplenism is a clinical syndrome in which normal splenic function becomes excessive as the spleen and MPS tissues enlarge. It has the following criteria.
    - Splenomegaly
    - A deficiency of at least one or more of the peripheral blood cell lines
    - Normal or increased levels of bone marrow precursors
    - An expectation that splenectomy will resolve cytopenia
- Most common cause of hypersplenism is venous obstruction. As there are no valves in the portal venous system, an increase in portal pressure is immediately transmitted in the splenic venous sinuses. Impaired blood flow out of the cords causes splenic sequestration and hypersplenism.

Common causes of splenomegaly

Excessive antigenic stimulation

- Viral infections (CMV, infectious mononucleosis, AIDS)
- Bacterial infections (septicemia, endocarditis, enteric fever)
- Protozoal infections (malaria, visceral leishmaniasis, toxoplasmosis)
- Fungal infections (histoplasmosis)

Disorders of immune-regulation

- Idiopathic rheumatoid arthritis
- Systemic lupus erythematosis

Excessive destruction of blood cells

- Neonatal Rh or ABO incompatibility
- Thalassemia
- Hereditary spherocytosis
- Sickle cell anemia

Neoplastic infiltration

- Acute leukemia
- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Neuroblastoma
- Histiocytosis X

Disorders of splenic blood flow

- Hepatic cirrhosis
- Congestive cardiac failure

Infiltration with abnormal material

- Gaucher's disease
- Glycogen storage disease type III
- Niemann-Pick disease

Extramedullaryhematopoiesis

- Thalassemia major
- Osteopetrosis

LYMPHADENOPATHY

- Lymph nodes are individual encapsulated anatomical units of the MPS distributed along lymph vessels throughout the body.
- Normal lymph nodes usually do not exceed 2.5 cm in diameter and they are not warm, tender, fluctuant, red, and matted.
- Lymphadenopathy is caused by:
    - An increase in the number of normal lyphocytes and macrophages during a response to an antigen (e.g. viral and bacterial illness)
    - Nodal infiltration by inflammatory cells in response to an infection localized to the nodes themselves (e.g. lymphadenitis)
    - Proliferation of neoplastic lymphocytes or macrophages (e.g. lymphoma)
    - Infiltration of nodes by metabolite-laden macrophages in storage diseases (e.g. Gaucher's disease)
- Lymphadenopathy is generalized when there is enlargement of two or more non-contagious lymph node regions. Hepatosplenomegaly is often an associated finding in disorders causing generalized lymphadenopathy.
- Involvement of a single or multiple contagious nodal regions constitutes regional lymphadenopathy. Infections are the most common cause of regional lymphadenopathy.
- Viral infections (especially common viral upper respiratory infections) are the most common cause of lymphadenopathy. In viral infections, lymph nodes are usually soft and mildly tenser. In bacterial infections, lymph nodes are more tender, warm, and sometimes red and fluctuant. Bacterial infection may be acute (e.g. septicemia, typhoid fever) or of long duration (e.g. tuberculosis).
- Lymphadenopathy due to malignant diseases is usually non-tender and is not associated with overlying redness. In such a case, lymph nodes have a rubbery texture, and group of nodes may be matted together. Lymphadenopathy is present in about 70% of patients with acute lymphoblastic leukemia. Non-Hodgkin's lymphoma is usually associated with bilateral

- Involvement of the spine may result in collapse of the vertebral body and may cause secondary compression of the spinal cord.
- In flat and long bones, osteolytic lesions with sharp borders occur.
- Lesions that involve weight-bearing long bones may cause pathologic fractures.
- Chronically draining, infected ears are commonly associated with destruction in the mastoid area.
- Bone destruction in the mandible and maxilla may result in free floating teeth on radiographs.
- About 50% of patients experience skin involvement (a hard-to-treat scaly, papular, seborrheic dermatitis of the scalp, diaper, axillary, or posterior auricular regions).
- Localized or disseminated lymphadenopathy or hepatosplenomegaly may be present.
- Exophthalmos may be present (often bilateral). It is caused by retro-orbital accumulation of granulomatous tissue.
- Gingival mucous membranes may be involved and appear like candidiasis.
- Otitis media is present in about 30% of patients. This may lead to deafness and destructive lesions of the middle ear.
- Pulmonary infiltrates are present on radiographs of 10–15% cases.
- Growth retardation is due to pituitary dysfunction or hypothalamic involvement.
- Other clinical findings are :
    - Diabetes insipidus
    - Panhypopituitarism
    - Primary hypothyroidism
- Bone marrow involvement may cause anemia and thrombocytopenia.
- Two serious manifestations of LCH are:
    - Hepatic involvement (leading to fibrosis and cirrhosis).
    - A Central Nervous System (CNS) involvement characterized by ataxia, dysarthria, and other neurologic symptoms.

Diagnosis

- Tissue biopsy is diagnostic. It is usually performed on skin or bone lesions.
- A thorough clinical and laboratory evaluation is helpful for diagnosis.
- Laboratory evaluation include:
    - Complete blood cell count
    - Liver function tests
    - Coagulation studies
    - Skeletal survey
    - Chest radiograph
    - Measurement of urine osmolality to rule out diabetes insipidus
    - Detailed evaluation of any organ system that has been shown to be involved by physical examination

Management

- The clinical course is usually benign if one system is involved. There is a high chance of spontaneous remission. So, minimal treatment is needed in many cases.
- Treatment is directed at arresting the progression of a bone lesion which may cause permanent damage.
- This includes curettage, steroid injection or low-dose local radiation therapy.
- Multisystem disease is treated with systemic multi-agent chemotherapy. These mainly include vinblastine and steroids, both of which have been found to be very effective in treating LCH.
- Late (fibrotic) complications (hepatic or pulmonary) are irreversible and require organ transplantation.

Prognosis

- The clinical course of single-system disease (bone, lymph node, or skin) generally is benign, with a high chance of spontaneous remission.
- The response rate to therapy is quite high, and mortality in severe LCH has been reduced by multiagent chemotherapy.

SPLENOMEGALY

- Splenomegaly is the most frequent and important clinical problem involving the spleen.
- Spleen is the largest lymph node in the body and contains a rich supply of mononuclear-phagocyte tissue. It provides resistance to infection and filters the formed elements of blood.
- Spleen has to enlarge 2–3 times its normal size before it can be palpable below the left costal margin.
- A palpable spleen is not unusual in a normal child. In about 30% of full-term neonates and 15% of infants less than 6 months of age, spleen tip is palpable up to 1–2 cm. A less than 1 cm spleen is palpable in about 1% of older children and adolescents.
- Commonly, splenomegaly in children is due to hyperplasia of the Mononuclear-Phagocyte System (MPS). There is excessive antigenic stimulation, disorders of immuno-regulation, or excessive destruction of abnormal blood cells.
- In infections, there is excessive antigenic stimulation and it is the most common cause of splenomegaly in children. Commonly, these are viral (CMV, EBV), bacterial (septicema, enteric fever, infective endocarditis), and protozoal (malaria).
- In about 50% of children with acute lymphoblastic leukemia (the most common malignancy in childhood), there is splenomegaly. Splenomegaly is frequently found in Hodgkin's disease and non-Hodgkin's

lymphadenopathy. Hodgkin's disease usually has unilateral involvement.

- Cervical lymph nodes are normally palpable in children after early infancy. These are the most common sites of abnormal lymphadenopathy. Most common cause is upper respiratory tract infections.
- Axillary lymph nodes are normally palpable in 90% of children. Inguinal lymph nodes are also normally palpable in children. Absence of normally palpable cervical or inguinal lymph nodes in children is unusual and may give a clue to an underlying immune deficiency.
- Malignancies and tuberculosis are common cause of mediastinal lymphadenopathy. Unilateral hilar lymphadenopathy is most commonly caused by tuberculosis.

Common causes of lymphadenopathy

Viral infections

- Common upper respiratory tract infections
- Infectious mononucleosis
- Cytomegalovirus
- Rubella
- Measles
- Varicella
- AIDS

Bacterial infections

- Septicemia
- Tuberculosis
- Typhoid fever
- Streptococcal pharyngitis (cervical)

Protozoal infections

- Toxoplasmosis

Abnormal proliferation of cells

- Acute leukemia
- Lymphoma
- Neuroblastoma
- Histiocytosis X

Autoimmune disorders and hypersensitivity states

- Idiopathic rheumatoid arthritis
- Systemic lupus erythematosis
- Drug reactions (isoniazide, phenytoin)

Storage diseases

- Gaucher's disease
- Niemann-Pick disease

CHAPTER 18

Immunologic Disorders

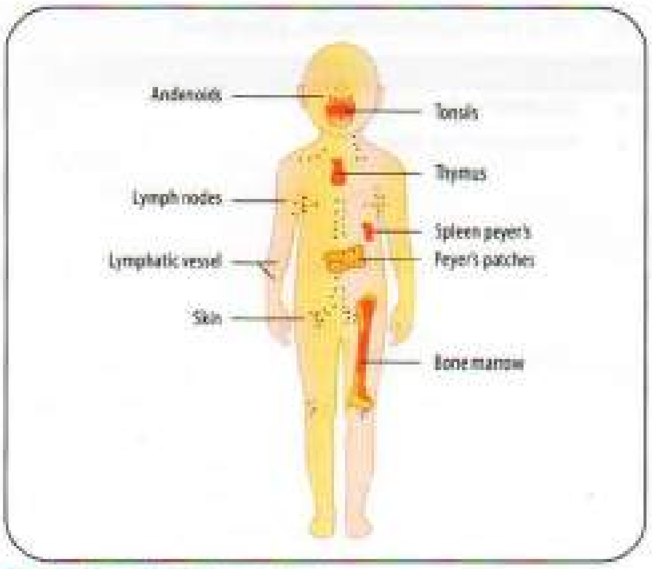


Figure 18.1: The immune System.

- Immunodeficiency is an abnormality of the immune system that renders a person susceptible to diseases normally prevented by a normal functioning immune system.

Primary or congenital immunodeficiency

- It is inherited due to mutation in genes controlling immune cells.

Secondary or acquired immunodeficiency

- Acquired as a consequence of other diseases or environmental factors (e.g. infections, malignancy, drugs)
- Acquired immunodeficiency syndrome due to human immunodeficiency virus

EVALUATION OF SUSPECTED IMMUNODEFICIENCY

Immunodeficiency is suspected when there is:

- Increased frequency, severity and duration of infections (e.g. recurrent respiratory or skin infections)
- Unexpected complications and unusual manifestations of infections (e.g. persistent sinus infections)
- Infections with organisms normally considered of low pathogenicity (opportunistic infections)
- Paucity of lymphoid tissue lymph nodes and tonsils).
- Failure to thrive
- Oral and perineal candidiasis (recurrent fungal or yeast infections)
- Malabsorption and recurrent diarrhea

Clinical evaluation

- **B-cell defects:** Recurrent pyogenic infections with extracellular encapsulated organisms, such as *Streptococcus pneumonia, Haemophilusinfluenzae*type b, and group A streptococcus, otitis, sinusitis, recurrent pneumonia, bronchiectasis, and conjunctivitis.
- **Complement defect:** Susceptibility to recurrent infections with *Neisseria meningitides*.
- **T-cell defect:** Recurrent infections with less virulent or opportunistic organisms, such as fungi, *Candida* sp, mycobacteria, viruses, and protozoa as well as bacteria. Growth retardation, malabsorption, diarrhea, and failure to thrive are common.
- **Neutrophil defect:** Recurrent dermatologic infections. Subcutaneous, lymph node, lung, and liver abscesses. Pulmonary infections common, including abscess and pneumatocele formation, contributing to chronic disease. Bone and joint infection common. Delayed separation of umbilical cord. Absence of pus at site(s) of infection. Poor wound healing.

Laboratory evaluation

- If the ESR is normal, chronic bacterial or fungal infection is unlikely.
- If the infant's neutrophil count is persistently elevated to extreme levels in the absence of any signs of infection, a leukocyte adhesion deficiency should be suspected.
- If the absolute neutrophil count is normal, congenital and acquired neutropenias and leukocyte adhesion defects are excluded.
- If the absolute lymphocyte count is normal, the patient is not likely to have a severe T-cell defect (T-cell absence results in striking lymphopenia).
- Absence of Howell-Jolly bodies rules out congenital asplenia.
- Normal platelet size or count excludes Wiskott-Aldrich syndrome.
- A simple screening test for B-cell defects is the measurement of serum IgA.
  - If the IgA level is normal, selective IgA deficiency, which is the most common B-cell defect, is excluded.
- Very high serum concentrations of one or more immunoglobulin of one or more immunoglobulin classes suggest:
  - HIV infection
  - Chronic granulomatous disease

- B-cells are absent in X-linked agammaglobulinemia, and present in common variable immunodeficiency, IgA deficiency, and hyperigM syndromes.
- The Candida skin testis the most effective test of T-cell function.
- Natural Killer (NK) cells can be enumerated by flow cytometry. Leukocyte adhesion deficiencies can be easily diagnosed by flow cytometric assays of blood lymphocytes or neutrophils, using monoclonal antibodies to CD18 or CD11 (LAD1) or to CD15 (LAD2).
- The most effective screening test for complement defects is a CH50 assay. Genetic deficiencies in the complement system are usually characterized by extremely low CH50 values.

CLASSIFICATION OF IMMUNODEFICIENCY DISORDERS

Primary B-cell immunodeficiency

- X-linked agammaglobulinemia
- Selective IgA deficiency

Primary T-cell immunodeficiency

- DiGeorge syndrome
- Ataxia telangiectasia
- Wiskott-Aldrich syndrome
- Acquired immunodeficiency
- Chemotaxis deficiency
- Chronic granulomatous disease
- Chediak-higashi syndrome
- Leukocyte adhesion deficiency
- Complement system deficiency

X-LINKED AGAMMAGLOBULINEMIA

- Patients with X-Linked Agammaglobulinemia (XLA), or Brutonagammaglobulinemia,have a profound defect in B-lymphocyte development.
- There is:
  Severe hypogammaglobulinemia
  - An absence of circulating B cells
  - Small to absent tonsils
  - No palpable lymph nodes

Clinical findings

- Most boys with XLA remain well during the first 6–9 months of life. This is due to maternally transmitted IgG antibodies.
- Thereafter, they get infections mostly with extracellular pyogenic organisms, such as *Streptococcus pneumonia* and *Haemophilus influenza*.
- Common infections include sinusitis, otitis media, pneumonia, or, less often, sepsis or meningitis.
- Chronic fungal infections are seen.

Differential diagnosis

- Acrodermatitisenteropethica
- Ataxia telangiectasia
- Common variable immunodeficiency
- Dermatologic manifestations of vitamin A deficiency
- Atopic dermatitis
- Severe combined immunodeficiency

Diagnosis

- lymphoid hypoplasia is found on physical examination:
  - Minimal or no tonsillar tissue
  - No palpable lymph nodes
- Serum concentrations of IgG, IgA, IgM, and IgE are far below the 95% confidence limits.
- Usually total immunoglobulins is <100 mg/dL.
- Levels of natural antibodies to type A and B red blood cell polysaccharide antigens (isohemagglutinins) and antibodies to antigens given during routine immunizations are abnormally low.
- Flow cytometry is an important test to demonstrate the absence of circulating B cells.

Management

- No curative therapy exists.
- Judicious use of broad spectrum antibiotics to treat documented infections.
- Regular administration of immunoglobulins (IVIG) to provide missing antibodies. IVIG is given at a dose of 400 mg/kg per monthtoachieve IgG levels close to the normal range.
- Chronic dermatologic manifestations of atopic dermatitis and eczema are controlled with daily moisturizing lotions and topical steroids.
- Hematopoietic stem cell transplantation.

COMMON VARIABLE IMMUNODEFICIENCY

- Common Variable Immunodeficiency (CVID) is characterized by hypogammaglobulinemia with phenotypically **normal B cells**.
- Usually, this condition (infections) presents late so it is also called acquired hypogammaglobulinemia.
- Patients presents with infections similar clinically to those with XLA.
- The sex distribution in CVID is almost equal.
- Age at onset is late, although it may be present in infancy.
- Infections may be less severe as compared to XLA.

Clinical findings

- Serum immunoglobulin and antibody deficiencies in CVID are profound.
- Children with CVID have autoantibody formation. There are normal sized or enlarged tonsils and lymph nodes. About 25% of patients have splenomegaly.
- Recurrent or chronic infections include pneumonia, sinusitis, otitis media, and diarrhea (bacterial, giardiasis).
- Repeated pulmonary infections may produce bronchiectasis.

- Sepsis and meningitis with encapsulated bacteria occur frequently.

Associations

- A sprue-like enteropathy with or without nodular follicular lymphoid hyperplasia of the intestine.
- Thymoma
- Alopecia areata
- Hemolyticanemia
- Gastric atrophy
- Achlorhydria
- Thrombocytopenia
- Pernicious anemia
- Lymphoid interstitial pneumonia
- Intestinal lung disease
- Pseudolymphoma
- B-cell lymphomas
- Amyloidosis
- Noncaseatingsarcoid-like granulomas of the lungs, spleen, skin, and liver
- Many-fold increase in lymphomas among affected women

DIGEORGE SYNDROME (THYMIC HYPOPLASIA)

CASE

A 9-month-old boy with ***characteristic facies*** (wide-set eyes, a prominent nose, and a small mandible) presents with ventricular septal defect (***murmur***), hypocalcemia (***seizures***), and ***recurrent infections***. Investigations show normal serum IgG, IgA and IgM. ***T-cell function*** is ***decreased.*** Parathyroid function is also decreased. On chest X-ray, there is no apparent thymus.

- Patients with **defects in T-cell function** have more **severe infections** or other clinical problems than in patients with antibody deficiency disorders.

Definition

- DiGeorge syndrome is a birth defect that is caused by an abnormality in chromosome 22 and affects the child's immune system.
- The disorder is marked by absence or underdevelopment of the thymus and parathyroid glands.
- Other structures forming at the same age are also frequently affected, resulting in:
    - Anomalies of the great vessels (right-sided aortic arch)
    - Esophageal atresia
    - Bifid uvula
    - **Congenital heart disease** (conotruncal, atrial, and ventricular septal defects)
    - A short philtrum of the upper lip, hypertelorism
    - An antimongoloid slant to the eyes
    - Mandibular hypoplasia
    - Low-set, often notched ears
- The diagnosis is often first suggested by **hypocalcemic seizures** during the neonatal period.

Clinical findings

- The child is born with a defective immune system and an abnormally low level of calcium in the blood.
- These defects usually become apparent within 48 hours of birth. The infant's heart defects may lead to heart failure, or there may be seizures and other evidence of a low level of calcium in the blood (hypocalcemia).
- DiGeorge syndrome is also associated with an increased risk of autoimmune disorders. There is an association with Graves' disease, immune thrombocytopenic purpura, juvenile rheumatoid arthritis, and **severe eczema**.

Diagnosis

- Diagnosis of DiGeorge syndrome can be made by ultrasound examination around the eighteenth week of pregnancy, when abnormalities in the development of the heart or the palate can be detected.
- Another technique that is used to diagnose the syndrome before birth is called fluorescence in situ hybridization, or FISH. This technique uses DNA probes from the DiGeorge region on chromosome 22. FISH can be performed on cell samples obtained by amniocentesis as early as the fourteenth week of pregnancy. It confirms about 95% of cases of DiGeorge syndrome.
- Diagnosis of DiGeorge syndrome is suggested by the child's facial features at birth.
- The diagnosis can be confirmed by blood tests for calcium, phosphorus, and parathyroid hormone levels, and by the test for immune function.

Management

Hypocalcemia

- Hypocalcemia in DiGeorge patients is unusually difficult to treat. Infants are usually given calcium and vitamin D by mouth.

Heart defects

- Infants with life-threatening heart defects are treated surgically.

Defective immune function

- Children with DiGeorge syndrome should be kept away from crowds or other sources of infection.
- They should not be immunized with vaccines made from live viruses or given corticosteroids.
- There is option of transplantation of culture unrelated thymic tissue transplants or bone marrow. Immune function is improved but there is no T-cell production because they have no thymus.

Prognosis

- The prognosis is variable. Many infants with DiGeorge syndrome die from overwhelming infection, seizures, or heart failure within the first year.
- Infections resulting from severe immune deficiency are the second most common cause of death in patients with DiGeorge syndrome.
- Advances in heart surgery indicate that the prognosis is most closely linked to the severity of the heart defects and the partial presence of the thymus gland.
- In most children who survive, the number of T cells in the blood rises spontaneously as they mature.
- Survivors are likely to be mentally retarded, and to have other developmental difficulties, including seizures or other psychiatric and neurological problems in later life.

Prevention

- Genetic counseling is recommended for parents of children with DiGeorge syndrome because the disorder can be detected prior to birth.

SEVERE COMBINED IMMUNODEFICIENCY (SCID)

CASE

A 7-month-old girl presents with failure to thrive and persistent pneumonia. Child was well at birth. Severe, ***recurrent diarrhea*** began at about 6 weeks of age. At 8 weeks the child developed ***recurrent pneumonia*** which responded poorly to antibiotic therapy. She has ***thrush since birth*** (despite multiple courses of an oral antifungal). Physical examination shows a malnourished. There are bilateral crepitations, oral thrush, and a monilial-appearing rash in the diaper area. Total white blood cell count is 5200/mm^3 with 87% polymorphonuclear cells, 12% lymphocytes, and 1% eosinophils. Hemoglobin and platelets are normal. ***Serum immunoglobulin*** levels are ***low***.

Definition

- Severe Combined Immunodeficiency (SCID) is the most serious human immunodeficiency disorder.
- It is a group of congenital disorders in which both the humoral part of the patient's immune system (**B-cells**) and the cells involved in immune responses (**T-cells**) **fail to work properly**.
- Children with SCID are vulnerable to recurrent severe infections, retarded growth, and early death.

Incidence

- SCID is thought to affect between one in every 100,000 patients, and one in every 500,000 infants.

Pathophysiology

- Human immune system has three parts: cellular, humoral, and nonspecific.
- The cellular and humoral parts of the system are both needed to fight infections they recognize disease agents and attack them.
- The cellular system is composed of many classes of T-lymphocytes (white blood cells that detect foreign invaders called antigens).
- The humoral system is made up of B cells, which are the only cells in the body that make antibodies.
- In SCID, neither the cellular nor the humoral part of the immune system is working properly.
- All patients with SCID have very small thymuses (<1 g) that usually fail to descend from the neck, contain no thymocytes, and lack corticomedullary distinction or Hassall corpuscles.

Clinical findings

- For the first few months of life, a child with SCID is protected by maternal antibodies.
- As early as three months of age, however, the SCID child begins to suffer from mouth infections (thrush), chronic diarrhea, otitis media and pulmonary infections, including pneumocystis pneumonia.
- The child loses weight, becomes very weak, and eventually dies from an opportunistic infection.

Diagnosis

- SCID is diagnosed by the typing of T and B cells in the child's blood.
- B cells can be detected by immunofluorescence tests for surface markers (unique proteins) on the cells.
- T cells can be identified in tissue sections (samples) using enzyme-labeled antibodies.

Management

- SCID is a pediatric emergency.
- If untreated, death usually occurs during the first 2 years of life.
- Patients with SCID can be treated with antibiotics and immunoglobulin to protect them from infections, but these treatments cannot cure the disorder.
- Stem cell transplantation or gene therapy is currently regarded as effective standard treatments for SCID.

Approach to treatment of infections

B-cell immunodeficiency

- Intravenous Immunoglobulin (IVIG) 200–800 mg/kg.
- Before starting antibiotics, obtain specimens for culture and sensitivity test. Antibiotic selection is decided on the basis of sensitivity test.
- If there is any abscess formation, then incision and drainage is needed.

T-cell immunodeficiency

- Obtain specimens for culture and sensitivity before starting antibiotic therapy.
- Incision and drainage of abscess if present.
- Early antiviral treatment is needed for herpes simplex, cytomegalovirus, and varicella-zoster viral infections.

- Topical antimicrobial agents are useful in skin infections.

Approach to prevention of infections

B-cell immunodeficiency

- Maintenance Intravenous Immunoglobulin (IVIG) 400–800 mg/kg every 3–5 weeks is needed to control infections in immunoglobulin deficiency states.
- In chronic recurrent respiratory disease, postural drainage and chest physiotherapy is needed.
- For recurrent or chronic pulmonary or middle ear infections, prophylactic administration of ampicillin, penicillin, or trimethoprim-sulfamethoxazole is given to prevent infections.

T-cell immunodeficiency

- Prophylactic administration of trimethoprim-sulfamethoxazole.
- to lower concentration of gut flora, oral non-adsorbable antimicrobial agents are used.
- live virus vaccines or bacillus Calmette-Guérin vaccine are contraindicated.
- Tuberculosis screening is recommended to prevent the disease.

Prognosis

- Currently, there is no cure for SCID. Most untreated patients die before age two.

Prevention

- Genetic counseling is recommended for parents of a child with SCID.

Combined Immunodeficiency

- Combined Immunodeficiency (CID) is distinguished from SCID by the presence of low but not absent T-cell function.

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

CASE

A 7-month-old boy presents with ***poor weight gain*** for the past 4 months although feeding is adequate. Physical examination reveals an active, alert infant with a strong suck reflex. On examination, he is wasted. There is ***generalized lymphadenopathy*** with ***hepatomegaly***. He has ***severe oral candidiasis*** that is resistant to treatment.

Definition

- Acquired Immune Deficiency Syndrome (AIDS) is an infectious disease caused by the human Immunodeficiency Virus (HIV).
- AIDS is the advanced form of infection with the HIV virus, which may not cause recognizable disease for a long period after the initial exposure (latency).
- No vaccine is currently available to prevent HIV infection.
- Treatment is needed to improve the quality and length of life for AIDS patients. This is achieved by:
    - Slowing or stopping the replication of the virus
    - Treating or preventing infections and cancers that occur due to patient's weakened immune system

Risk factors

- AIDS can be transmitted in several ways. The risk factors for HIV transmission vary according to category:
- Sexual contact
- Transmission in pregnancy
    - The chances of transmitting the disease to the child are higher in women in advanced stages of the disease.
    - If mother is HIV positive, 100% of children will be test positive at birth. About 20% of these will remain HIV positive at one year of age.
    - Breastfeeding increases the risk of transmission by 10–20%.
    - The use of zidovudine (AZT) during pregnancy and cesarean section can decrease the risk of transmission to the baby.
- Exposure to contaminated blood or blood products.
- Needle sticks among health care professionals.
- HIV is not transmitted by handshakes or other casual non-sexual contact, coughing or sneezing, or by bloodsucking insects such as mosquitoes.
- As AIDS can be transmitted from an infected mother to the child during pregnancy, during the birth process, or through breast milk, all infants born to HIV-positive mothers are a high-risk group.
- Infants infected with HIV have a 20–30% chance of developing AIDS within a year and dying before age three. In the remainder, AIDS progresses more slowly. The average child patient survives to seven years of age.

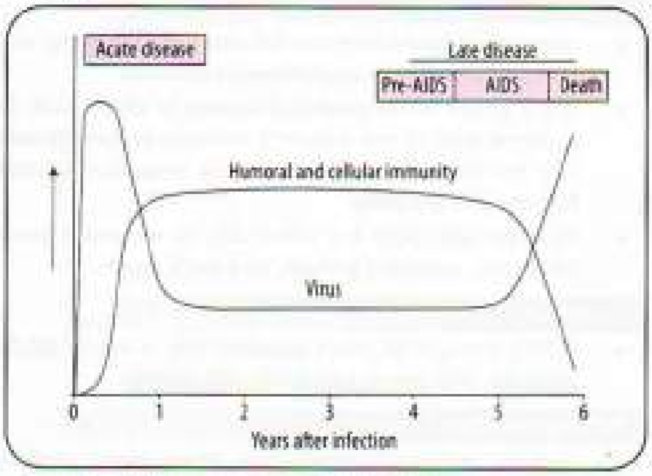


Figure 18.2: Pathogenesis of HIV infection.

- Because HIV destroys immune system cells, AIDS is a disease that can affect any of the body's major organ systems.

Clinical findings

- Many patients will develop low-grade fevers, chronic fatigue, and general weakness. HIV may also cause a combination of food malabsorption, loss of appetite, and increased metabolism that contribute to the so-called AIDS wasting.
- AIDS is usually marked by a very low number of CD4+ lymphocytes, followed by a rise in the frequency of opportunistic infections and cancers.
- The most common fungal disease associated with AIDS is Pneumocystis Jiroveci Pneumonia (PCP) (also known as P Carini/ PCP). PCP is the immediate cause of death in 15–20% of AIDS patients. It is an important measure of a patient's prognosis. Other fungal infections include oral thrush and cryptococcal meningitis.
- Toxoplasmosis is a common opportunistic infection in AIDS patients that is caused by a protozoan.
- AIDS patients may develop tuberculosis.
- Oral hairy leukoplakia is common.
- AIDS patients are likely to develop bacterial infections of the skin and digestive tract. Viruses. AIDS patients are highly vulnerable to Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), and Epstein-Barr virus (EBV) infections.
- Patients with late-stage AIDS may develop Kaposi's Sarcoma (KS). KS is the most common AIDS-related malignancy. It is characterized by reddish-purple blotches or patches on the skin or in the mouth. The second most common form of cancer in AIDS patients is a tumor of the lymphatic system (lymphoma).

Diagnosis

- Detection of antibody to HIV is the usual first step in diagnosing HIV infection.
- Recommendations for diagnosing infants include the following:
  - Because of the persistence of the maternal HIV antibody, infants younger than 18 months require virologic assays that directly detect HIV in order to diagnose HIV infection
  - Preferred virologic assays include HIV bDNA Polymerase Chain Reaction (PCR) and HIV RNA assays.
  - Further virologic testing in infants with known perinatal HIV exposure is recommended at 2 weeks, 4 weeks, and 4 months
- In older children and adults, an Enzyme-Linked Immunosorbent Assay (ELISA) to detect HIV antibody, followed by a confirmatory Western blot (which has increased specificity), should be used to diagnose HIV infection.
- Blood counts
- Viral load tests
- p24 antigen assays
- Tissue biopsies
- Samples of cerebrospinal fluid
- Imaging techniques, such as Magnetic Resonance Imaging (MRI) and Computed Tomography scans (CT) are used to diagnose AIDS-related cancers, some opportunistic infections, damage to the central nervous system, and wasting of the muscles.
- Urine and stool samples are used to diagnose infections caused by parasites.
- AIDS patients are also given blood tests for syphilis and other sexually transmitted diseases.

Management

- Psychosocial support is extremely important.
- There is no cure for AIDS.
- Anti-retroviral therapy can reduce the presence of the virus in the body but cannot eliminate it.

Treatment of opportunistic infections [illegible]

- Most AIDS patients require complex long-term treatment with medications for infectious diseases. This treatment is often complicated by the development of resistance in the disease organisms.
- AIDS-related malignancies in the central nervous system are usually treated with radiation therapy. Cancers elsewhere in the body are treated with chemotherapy.

Prophylactic treatment for opportunistic [illegible]

- Prophylactic treatment is treatment that is given to prevent disease. AIDS patients with a history of *Pneumocystis* pneumonia; with CD4+ counts below 200 cells/mm^3 or 14% of lymphocytes; weight loss; or thrush should be given prophylactic medications. Drugs given are trimethoprim-sulfamethoxazole, dapsone, pyrimethamine, and leucovorin. Dapson and pentamidine may be given in aerosol form.
- Meningococcal, influenza, pneumococcal, hepatitis B vaccines are given.

Anti-Retroviral Treatment (ART)

- **Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTIs):** These drugs work by interfering with the action of HIV reverse transcriptase inside infected cells, thus ending the virus' replication process. These drugs include zidovudine (AZT), didanosine (ddI), zalcitabine (ddC), stavudine (d4T), lamivudine (3TC), and abacavir (ABC).
- **Protease Inhibitors (PIs):** Protease inhibitors can be effective against HIV strains that have developed resistance to nucleoside analogues, and are often used in combination with them. These compounds include saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir.
- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** This is a new class of antiretroviral agents.

Three are available, nevirapine, which was approved first, delavirdine and efavirin.

- **Fusion inhibitors:** The newest class of antiretrovirals. They block specific proteins on the surface of the virus or the CD4 cell. These proteins help the virus gain entry into the cell. Common fusion inhibitor used is enfuvirtide.
- **CCR5 coreceptor antagonists (entry inhibitors)**
- **HIV integrase strand transfer inhibitors**

Treatment protocol

- Combination ART with at least 3 drugs from at least 2 classes of drugs is recommended for initial treatment.
- It provides the best opportunity to preserve immune function and delay disease progression.
- Drug combinations for initial therapy in children include 2 NRTIs plus 1 NNRTI or 1 PI.
- Infected infants who have clinical symptoms of HIV disease or evidence of immune compromise should be treated.
- Patients aged 1 year or older with Acquired Immunodeficiency Syndrome (AIDS) or significant symptoms should be aggressively treated regardless of $CD4^+$ percentage and count or plasma HIV RNA level.

Stimulation of blood cell production

- Because many patients with AIDS suffer from abnormally low levels of both red and white blood cells, they may be given medications to stimulate blood cell production. Erythropoietin may be given to anemic patients. Patients with low white blood cell counts may be given filgrastim or sargramostim.

Treatment in women

- Treatment of pregnant women with HIV is particularly important in that anti-retroviral therapy has been shown to reduce transmission to the infant by 65%.
- Breastfeeding by HIV-infected women (including those receiving antiretroviral drugs) is not recommended.

Prognosis

- At present, there is no cure for AIDS.
- Anti-retroviral drugs help reduce the HIV amount in the blood to an undetectable level.
- The use of multi-drug therapies has significantly reduced the numbers of deaths resulting from AIDS.
- Prognosis depends on the patient's specific symptoms and the organ systems affected by the disease.
- Patients with AIDS-related lymphomas of the central nervous system die within two to three months of diagnosis; those with systemic lymphomas may survive for eight to ten months.

Prevention

- Individuals must be instructed to practice safe sex.
- Avoiding needle sharing among intravenous drug users.
- Blood and blood products should be carefully monitored.
- Healthcare professionals must take all necessary precautions by wearing gloves and masks when handling body fluids and preventing needle-stick injuries.
- Women should be tested for HIV during routine prenatal testing.

WISKOTT-ALDRICH SYNDROME

IMMUNODEFICIENCY WITH THROMBOCYTOPENIA AND ECZEMA

CASE

A 4-month-old child presents with failure to thrive, chronic diarrhea, ***eczema***, and ***recurrent serious bacterial, fungal, and viral infections***. Laboratory findings show serum IgG, IgA, IgM (***low***), thrombocytopenia, T-cell function (decreased), and parathyroid function (normal).

- Wiskott-Aldrich syndrome, an X-linked recessive syndrome

Clinical findings

- **Thrombocytopenia** (Prolonged bleeding from the circumcision site or bloody diarrhea during infancy).
- **Combined immunodeficiency** (recurrent susceptibility to infections)
    - ○ Decreased IgM levels
    - ○ Decrease T-cell numbers and function
    - ○ Impaired response to polysaccharide antigens
- **Eczema** (atopic dermatitis)
- Recurrent infections usually develop during the 1st year of life (otitis media, pneumonia, meningitis, and sepsis).
- Infections, bleeding, and EBV-associated malignancies are major causes of death.

Differential diagnosis

- Other disorders causing thrombocytopenia
- Severe eczematous disorders
- Other immune deficiency disorders

Diagnosis

- Clinical phenotype
- Platelet count morphology
- X-linked pedigree
- Mutation analysis of the WASP (Wiskott-Aldrich Syndrome Protein) gene

Management

- It is oriented to different clinical problems (bleeding, infections, and eczema)
- Good supportive care
- Appropriate nutrition

- Intravenous Immunoglobulins (IVIG) 2 g/kg
- Use only killed vaccines.
- Aggressive management (topical care) of eczema and associated cutaneous infections.
- Platelet transfusion for serious bleeding episodes.
- Prophylaxis with antibiotics including trimethoprim sulfamethoxazole for *P carinii*.
- Splenectomy is helpful in improving platelet count if a bone marrow transplant is not going to be done.
- High-dose IVIG with systemic steroids for autoimmune complications.
- Treatment of choice is bone marrow or cord blood transplantation and is usually curative.
- Monitor for malignancy.

ATAXIA-TELANGIECTASIA

CASE

A 4-year-old child presents with ***ataxia*** and irregular eye movements for last one year. On clinical examination of eyes, he has ***telangiectasias***. There is also history of recurrent respiratory infections.

- Ataxia-telangiectasia is a complex syndrome with immunologic, neurologic, endocrinologic, hepatic, and cutaneous abnormalities.
- Ataxia-telangiectasia progressively destroys part of the motor control area of the brain, leading to a lack of balance and coordination.
- Cells of patients have increased sensitivity to ionizing radiation, defective DNA repair, and frequent chromosomal abnormalities.

Clinical findings

- Ataxia-telangiectasia is an autosomal recessive disorder.
- Common problems are:
  - Progressive cerebellar ataxia
  - Oculocutaneoustelangiectasias
  - Chronic sinopulmonary disease
  - High incidence of malignancy
  - Variable humoral and cellular immunodeficiency
- Infants with Ataxia-telangiectasia initially often appear very healthy.
- At around age two, ataxia and nervous system abnormalities become apparent.
- The root cause of Ataxia-telangiectasia associated ataxia is cell death in the brain, specifically the large branching cells of the nervous system (Purkinje's cells) that are located in the cerebellum.
- A child becomes clumsy, loses balance easily and lacks muscle control. Speech becomes slurred and more difficult, and the symptoms progressively worsen.
- Between ages 2–8 years, telangiectasia appears on the cheeks and ears and in the eyes.
- By age 10–12, children with Ataxia-telangiectasia can no longer control their muscles.
- Immune system deficiencies become common, and affected individuals are extremely sensitive to radiation.
- Immune system deficiencies vary between individuals but include lower than normal levels of immunoglobulins and white blood cells. The most frequent humoral immunologic abnormality is the selective absence of IgA.
- The thymus gland, which aids in development of the body's immune system, is either missing or has developed abnormally.
- Intelligence is normal, but growth may be retarded due to immune system or hormonal deficiencies.
- Individuals with Ataxia-telangiectasia may have diabetes, prematurely graying hair, and difficulty swallowing.
- As the children grow older recurrent respiratory infections and blood cancers, such as leukemia or lymphoma, are common.

Diagnosis

- Diagnosis relies on recognizing progressive ataxia and telangiectasia. However, this may be difficult as ataxia symptoms do appear prior to telangiectasia symptoms by several years.

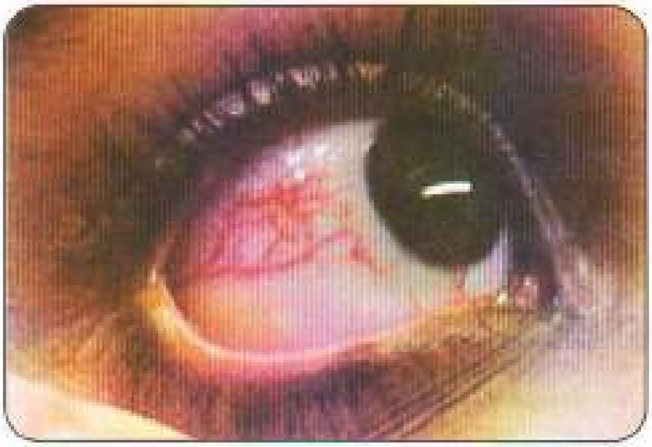


Figure 18.3: Ocular telangiectasia.

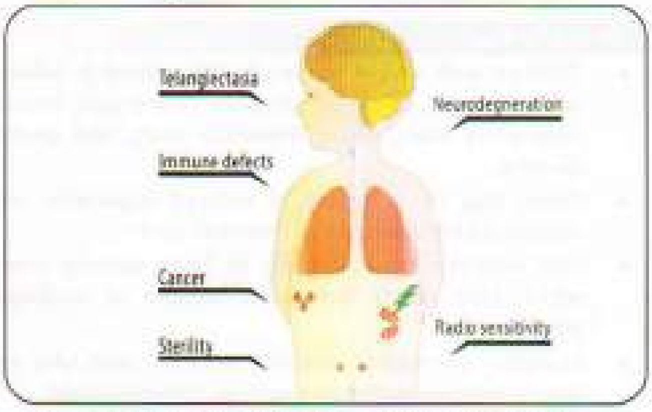


Figure 18.4: Clinical features of ataxia telangiectasia.

Management

- There is currently no cure for Ataxia-telangiectasia.
- Treatment focuses on managing the individual's multiple symptoms.
- Physical therapy and speech therapy can help the patient adjust to ataxia.
- Intravenous immunoglobulins are needed to strengthen the weakened immune system.
- High-dose vitamin administrations may also be helpful.

Prognosis

- Ataxia-telangiectasia is a fatal condition.
- Children with ataxia-telangiectasia become physically disabled by their early childhood and typically die by about 20 years of age usually from the associated blood cancers and malignancies.

LEUKOCYTE ADHESION DEFICIENCY

CASE

A ***5-week-old*** infant presents with ***still attachedumbilical cord***. Otherwise he is normal with no illness or fever. On clinical examination, he has a cord without evidence of separation. He also has a ***wound*** on head since birth which is ***slowly healing***.

- Leukocyte Adhesion Deficiency (LAD) is an autosomal recessive disorder of leukocyte function.
- LAD is characterized by recurrent bacterial and fungal infections and depressed inflammatory responses despite striking blood neutrophilia.
- Neutrophils have significant defects in adhesion, motility, and ability to phagocytose bacteria.

Pathogenesis

- Because of their inability to adhere firmly to intercellular adhesion molecules on inflamed endothelial cells, neutrophils cannot transmigrate through the vessel wall and move to the site infection.
- Neutrophils that reach at inflammatory sites fail to recognize microorganisms, resulting in impaired phagocytic function and high risk for serious and recurrent bacterial infections.

Clinical findings

- Children with severe forms of LAD present in infancy with recurrent bacterial infections of the skin, mouth, respiratory tract, lower intestinal tract, and genital mucosa.
- There may be a history of delayed separation and associated infection of the umbilical cord.
- Skin infection may progress to large chronic ulcers which heal slowly and need months of antibiotic treatment.
- Common pathogens infecting patients with LAD are *Staphylococcus aureus*and such as *Escherichia coli*.
- There are also opportunistic infections by fungi such as *Candida* and *Aspergillus*.
- Typical signs of inflammation, such as swelling, erythema, and warmth, are usually absent.
- Pus does not form.
- Few neutrophils are identified microscopically in biopsy specimens of infected tissues.

Diagnosis

- Significant neutrophilicleukocytosis, often $>25{,}0000/\text{mm}^3$, is a prominent feature.
- Flow cytometric test in stimulated and unstimulated neutrophils. Neutrophil and monocyte adherence, aggregation, chemotaxis, and phagocytosis show abnormalities.

Management

- Early allogeneic Hematopoietic Stem Cell Transplantation (HSCT) is the treatment of choice.
- Otherwise treatment is largely supportive.
- Prophylactic trimethoprim-sulfamethoxazole.
- Early identification and treatment of infections with broad-spectrum antibiotics.

Prognosis

- It depends on type and severity of the disease.
- Patients with severe deficiency may die in infancy.
- Surviving older children have a susceptibility to severe life threatening systemic infections.

CHRONIC GRANULOMATOUS DISEASE

CASE

A 2-year-old boy presents with ***recurrent skin lesions*** (abscess formation) requiring incision and drainage three times. There is also past history of recurrent thrush, candida diaper dermatitis and fever. Ultrasound reveals two ***abscesses in the liver***. X-ray knee shows ***osteomyelitis***. Serum immunoglobulins are raised. Blood culture and sensitivity is positive. There is lack of superoxide production in DHR test.

- Chronic Granulomatous Disease (CGD) is an inherited disorder in which white blood cells lose their ability to destroy certain bacteria and fungi.
- CGD is an X-linked recessive genetic disease.
- Neutrophils and monocytes are capable of normal chemotaxis, ingestion, and degranulation, but are unable to kill catalase positive microorganisms.
- There is a defect in the generation of microbicidal oxygen metabolites.

Clinical findings

- Symptoms of the disease usually appear by age two.
- Frequent, recurrent infections of the skin, lungs (e.g. pneumonia), mouth (e.g. gingivitis), nose, intestines and lymph nodes are a hallmark of this disease.

- Patients may also develop multiple, recurrent liver abscesses and bone infections (osteomyelitis).

Diagnosis

- Diagnosis is based on the observation of a pattern of recurrent infections.
- Blood tests of lymphocyte and antibody functions will be normal.
- Tests of phagocytic cells will show normal ingestion, but a greatly decreased ability to kill bacteria.
- The diagnosis is made by performing flow cytometryusing dihydrorhodamine 123 (DHR) to measure oxidant production.

Management

- There is no cure for the underlying cause of chronic granulomatous disease.
- Early, aggressive treatment of all infections is critical to the successful management of CGD. Patients are treated with antibiotics and immunoglobulins. Antibiotics are used at the first sign of infection.
- Patients with CGD should be given daily oral trimethoprim sulfamethoxazole to reduce the number of bacterial infections.
- Interferon gamma is a treatment for CGD that has shown promising results. Interferon-□50 μg/m^{2}three times/week significantly reduces the number of serious infections.
- Itraconazole administered prophylactically reduces the frequency of fungal infections.
- Most abscesses require surgical drainage.
- Corticosteroids may be useful for the treatment of children with antral and urethral obstruction or severe granulomatous colitis and to shrink the granulomas in the lung.
- Stem cell transplantation may be curative.

Prognosis

- Although antibiotics can prevent or treat most infections, premature death may result, typically due to repeated lung infections.

CHAPTER 19

Endocrine Disorders

GROWTH HORMONE DEFICIENCY

CASE

Growth hormone deficiency due to brain tumor: A 4-year-old boy presents with a history of ***headache*** and ***vomiting*** for last one month. His ***growth*** has been ***slowed*** for the last one year. On examination, he is below the 3rd centile for height, on the 10th for weight. There is ***papilledema*** on fundoscopy.

- Growth Hormone (GH) is an anabolic hormone that stimulates growth of all tissues. It is secreted in a pulsatile fashion, more during sleep and exercise.
- Its most important effect is on the growth of long bones. Its action on long bone growth is mediated through another hormone IGF-I (insulin like growth factor-1), which is generated in the liver and other tissues.
- Growth hormone is released from the pituitary gland when stimulated by the hypothalamic hormone, Growth Hormone Releasing Factor (GRF). GH promotes linear growth, bone thickness, protein synthesis, insulin resistance and increases blood glucose.

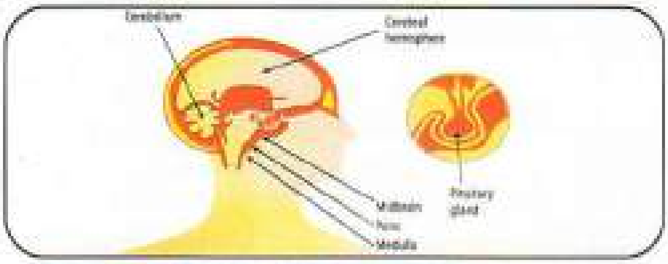


Figure 18.1 : Anatomy of pituitary gland

- Growth hormone deficiency is associated with a variety of clinical conditions and syndromes. In Laron syndrome, there is end organ resistance to GH.

Idiopathic growth hormone deficiency

- It is the most common cause of growth hormone deficiency.
- Usually, the defect is in the hypothalamus, resulting in deficient Growth Hormone Releasing Factor (GRF) stimulation of pituitary gland.
- Growth hormone is not necessary for fetal growth. So, the affected newborns are of normal size. Growth velocity slows after 6–12 months of age.
- Male infants have microphallus secondary to intrauterine gonadotropin deficiency.
- There may be symptomatic hypoglycemia in newborn.
- Older children with idiopathic growth hormone deficiency have very short stature (growth velocities of less than 5 cm/year). There is mild truncal adiposity, frontal bossing, a flat nasal bridge, and a high-pitched voice.

Secondary growth hormone deficiency

- Secondary to CNS tumors
- Trauma
- Surgery involving the hypothalamus or pituitary gland
- Irradiation
- Infectious infiltration

Differential diagnosis

- Constitutional growth delay
- Hypothyroidism
- Syndrome associated—Down, Turner, Prader-Willi, Russel-Silver dwarfism, skeletal dysplasia syndromes, many others
- Psychosocial short stature—emotional deprivation
- Chronic systemic disease—inflammatory bowel and liver disease, celiac disease, glycogen storage disease, cardiac and renal insufficiency.
- Malnutrition.

Diagnosis

- Growth hormone provocative tests:
  - Diagnosis by noting ↓ GH response to insulin, arginine, levodopa, clonidine, or glucagon.
  - Growth hormone levels greater than 10 ng/ml after exercise or insulin induced hypoglycemia are considered evidence of normal growth hormone capacity.
  - Peak levels of 7–10 ng/ml are intermediate and indicate partial growth hormone deficiency or a neuro-secretary defect.
  - Levels less than 7 ng/ml on two provocative tests indicate classic growth hormone deficiency.
- Serum insulin-like growth factor (IGF-1) and IGF binding protein are reduced in GH deficiency.

Management

- Human recombinant Growth Hormone (GH) is given by subcutaneous injection daily or every other day.
- Exogenous GH is approved for GH deficiency, Turner syndrome, renal insufficiency prior to transplant, Prader-Willi syndrome, Small for Gestational Age (SGA) babies with failure of catch-up growth.
- Exogenous GH for constitutional growth delay is also approved.
- Rare side effects of GH therapy are intracranial hypertension, slipped capital femoral epiphysis.

SHORT STATURE

CASE

Growth Hormone (GH) deficiency: An 8-year-old boy presents with short stature. There is ***no significant medical history***. He is ***developmentally normal***. On examination, he has ***short stature***. Otherwise, his physical examination is normal. His upper and lower body segment measurements (***US/LS***) demonstrate ***normal body proportion***.

Definition

- Short stature is defined as subnormal height relative to other children of the same age, sex, ethnic background, and for family heights.
- The 3rd or 5th percentile of the growth curve is selected for demarcation, but pathologic short stature is usually 3.5 standard deviation below the mean.

Types

Children of short stature can be divided into two main groups:

1. Those who are small but are growing at an appropriate rate
2. Those who are small but are growing slowly

Etiology

1. Normal growth velocity

- Constitutional delay in growth and puberty
- Familial (genetic) short stature
- Low birth weight and intrauterine growth retardation

2. Low growth velocity

- Under-nutrition
- Psychosocial deprivation
- Chronic illness, e.g. renal (chronic renal failure, renal tubular acidosis), cardiovascular (congenital cyanotic heart disease, congestive cardiac failure), respiratory (severe asthma, cystic fibrosis)
- Malabsorption, e.g. Crohn's disease, celiac disease
- Syndromes, e.g. Turner's, Down, Prader-Willi
- Endocrine disease, e.g. Growth hormone deficiency, hypothyroidism, panhypopituitarism, Cushing syndrome (usually iatrogenic), poorly controlled diabetes mellitus
- Inborn errors of metabolism, rickets, mucopolysaccharidosis
- Constitutional (intrinsic) diseases of bone, e.g. achondroplasia, skeletal and spinal dysplasias, osteogenesisimperfecta

Assessment of a child with short stature

- Ask about the height of parents and siblings (familial short stature).
- Also ask whether the mother had a history of delayed menarche or father a delayed adolescence growth spurt (constitutional short stature).
- Obtain a detailed nutritional and psychosocial history.
- Identify predisposing conditions such as congenital infections, small for gestational age at birth (primordial short stature), congenital syndromes, chronic illness involving any organ system (especially the gastrointestinal, cardiac, pulmonary, and renal), and malnutrition.
- Document the accurate height, weight, head circumference, arm span, upper and lower body segment ratio of the child and plot these on the centile charts.
- Length in supine position is plotted for children from birth to 2 years of age.
- Standing height is plotted for children above 2 years of age.
- Disproportionate short stature indicates a skeletal dysplasia except osteogenesisimperfecta.
- Proportionate short stature is present in endocrine cases except in hypothyroidism.
- Visual field examination should be performed. Fundoscopy is performed to look for optic nerve abnormalities, which might indicate increased intracranial pressure or an underlying CNS disease causing growth hormone deficiency.
- Abnormalities of digits, joints, and body proportions should be noted.
- Note the presence or absence of a goiter.
- Evaluate the child's pubertal development (Tanner staging).
- Anomalies of genitalia should be noted.
- Assess the child's dentition and status of nutrition.
- Parental heights are also noted and mid-parental height and target height should be determined.
- Document the child's growth rate (growth velocity) from 1 year of age through pre-adolescence. The lower limit of normal growth is approximately 5 cm per year. A short child with a normal growth rate is unlikely to have significant illness or endocrinopathy.
- Rule out thyroid or growth hormone deficiency in children with a significant delayed bone age that are growing less than 4–5 cm a year.
- Consider Turner syndrome (XO genotype) in any short girl even those without typical Turner phenotype. Early diagnosis is important for appropriate therapy. GH therapy should be started at a young age and estrogen and progesterone at the time of puberty.

Investigations

- Choice of investigations depends upon the cause of short stature assessed by a detailed history, physical examination, and accurate measurements.
- Extensive investigations are often unnecessary if history and examination are normal and familial or constitutional causes are suspected.
- Initial investigations include complete blood counts, ESR, complete urine examination, blood urea and creatinine, thyroid function tests, and X-rays for bone age assessment.
- Other investigations include karyotyping (Turner syndrome); jejunal biopsy (celiac disease); serum

calcium, phosphate, and alkaline phosphate (rickets, hypoparathyroidism).

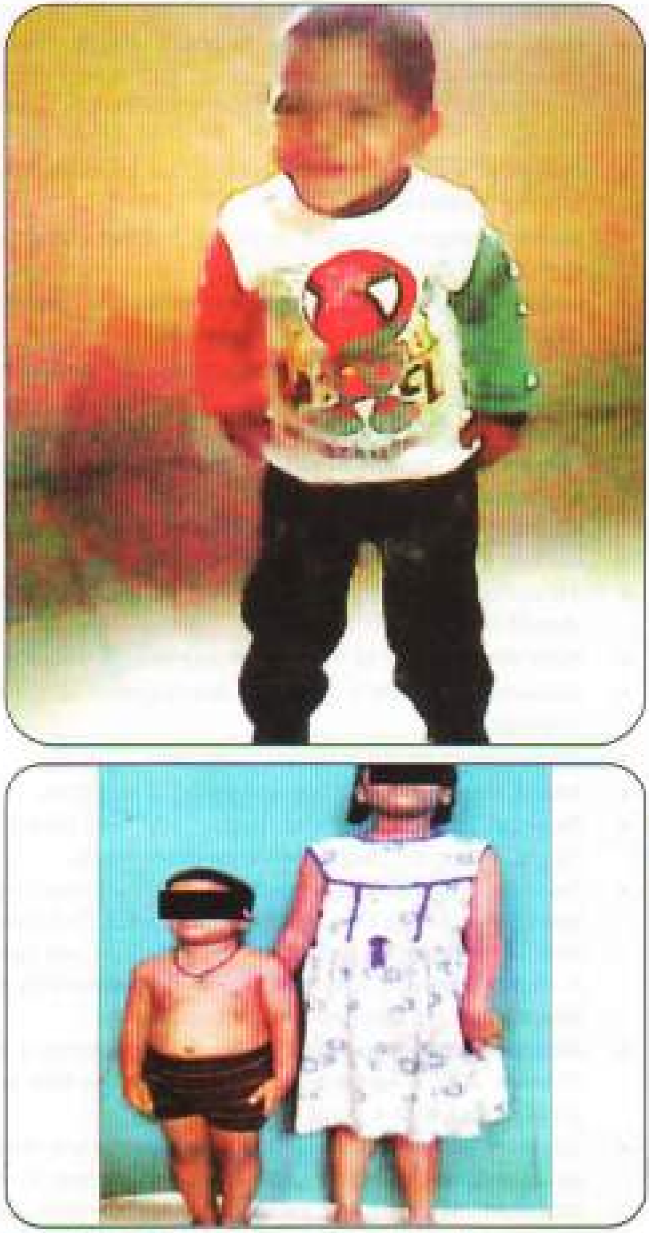


Figure 19.2: Short stature with hypothyroidism

Common causes of short stature

Constitutional delay of growth

CASE

A 14-year-old boy presents with ***short stature.*** He is developmentally normal. He has a ***normal past medical history***. He is the shortest boy in his class. His ***father began puberty at age 16*** and completed his growth at age 19 years; he is now ***6 feet tall.***

- Constitutional delay of growth means a delayed growth pattern with delayed maturity and normal final height.
- The condition occurs much more commonly in males than females.
- The child's rate of physical maturation is delayed compared with that of other children of the same age.
- The bone age is usually equal to the height age but is less relative to chronological age.
- Pubertal maturation is correspondingly delayed.
- The ultimate height of these children is usually normal for their families, since the pubertal growth spurt often occurs between 15 and 17 years, and growth continues until 18 to 20 years of age.
- Family members usually are of average height, but there often is a family history of short stature in childhood and delayed puberty in other family members.
- Reassurance that no significant endocrine disease exists and that normal growth and puberty with reasonable adult stature are expected is all that is required.
- Treatment with low doses of testosterone over a 3–6 month period in boys may be useful in hastening the timing of puberty and accelerating growth, but final adult height is not enhanced.
- Growth hormone does not have a place in treating these normal children.

Familial (genetic) short stature

- These children establish growth curves at or below the 5th percentile by 2–3 years of age.
- They are otherwise completely healthy, with a normal physical examination.
- They have growth rate greater than 4 cm per year, and have a bone age appropriate for chronological age.
- Puberty occurs at the usual age.
- Short stature usually is found in at least one parent.
- However, because the inheritance of height is complex, occasionally short stature may be present only in more distant relatives.
- Because puberty occurs at the expected time, these children seem to be less disturbed socially and emotionally as compared with constitutional delay.

Growth hormone deficiency

- Children with classic growth hormone deficiency grow at subnormal growth velocities (<5 cm/year) and have a significant delay of skeletal maturation.
- After establishing that current growth velocity is less than 5 cm/year and that thyroid function is normal and other systemic disease is unlikely, growth hormone testing should be carried out.
- Classic growth hormone deficient patient do not show an increase in serum growth hormone level after

stimulation by various secretagogues (insulin, clonidine).

- For growth hormone deficiency, recombinant human growth hormone is given.
- Acceleration of the height velocity from a baseline of less than 5 cm/year to at least 7–8 cm/year on replacement of growth hormone is confirmation of genuine deficiency.
- A poor response requires review of the diagnosis or compliance.

Hypothyroidism

- Hypothyroidism causes marked growth failure, with growth velocity less than 5 cm/year, and marked retardation of skeletal maturation.
- Because hypothyroidism is easily treatable, almost all children with short stature should have T_4, and TSH levels measured, even in the absence of obvious symptoms, to rule out any degree of hypothyroidism.
- Treatment is with thyroxine.

Chronic systemic disease

- The impact of chronic systemic disease on growth is well known.
- Cyanotic congenital heart disease, poorly controlled diabetes mellitus, gastrointestinal diseases (celiac disease, inflammatory bowel disease), chronic renal failure, and asthma have a deleterious effect on growth, related to a combination of nutritional deficits and increased metabolic demands created by the disease process.
- These children need treatment of primary disease with high caloric balanced diet.

Undernutrition

- On a global basis, malnutrition is the commonest cause of poor growth and short stature.
- Inadequate caloric intake may occur when a child is not offered enough to eat because of inadequate parenting or poverty.
- Adequate dietary advice is needed in such a case.

Psychosocial deprivation

- In some children, a hostile, abusive, or neglected environment appears to result in functional growth hormone deficiency.
- Children with psychosocial deprivation characteristically show bizarre behavior, disturbed sleep, and immature speech.
- Clinically, they may resemble children with growth hormone deficiency, with marked retardation of bone age and delayed puberty.
- Opinion of a child psychiatrist is needed.

Disproportionate short stature

- Skeletal dysplasias cause disproportionate short stature.
- Measurements of arm span and upper-to-lower body segment ratio are helpful in determining whether a child has normal body proportions.
- If disproportionate short stature is found, a skeletal survey may be useful because specific radiographic features characterize certain disorders.

PRECOCIOUS PUBERTY

CASE

A ***5-year-old girl*** presents with ***breast and pubic hair development*** for the last 4 months. On physical examination, she has height and weight above the 95th percentile (***tall stature***) oily skin, and ***facial acne***.

Definition

- Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys.
- Depending on the primary source of the hormonal production, precocious puberty may be classified as:
    1. Central (also known as gonadotropin dependent or true).
    2. Peripheral (also known as gonadotropin independent or precocious pseudopuberty).

Conditions causing precocious puberty

Central (GnRH-dependent) precocious puberty

- Idiopathic
- Central nervous system abnormalities
    - Acquired—abscess, chemotherapy, radiation, surgical trauma
    - Congenital—arachnoid cyst, hydrocephalus, hypothalamic hamartoma, septo-optic dysplasia, suprasellar cyst
    - Tumors—astrocytoma, craniopharyngioma, glioma

Peripheral (GnRH-independent) precocious puberty

- Congenital adrenal hyperplasia
- Adrenal tumors
- McCune-Albright syndrome
- Familial male-limited gonadotropin independent precocious puberty
- Gonadal tumors
- Exogenous estrogen—oral (contraceptive pills) or topical
- Ovarian cysts (females)
- HCG-secreting tumors (e.g. hepatoblastomas, choriocarcinomas) (males)

Incomplete (partial) precocious puberty

- Premature thelarche
- Premature adrenarche
- Premature menarche

Evaluation of precocious puberty

- Precocious puberty refers to the appearance of physical and hormonal signs of pubertal development at an earlier age than is considered normal.
- Central precocious puberty is defined by the onset of breast development before the age of 8 years in girls and by the onset of testicular development (volume ≥4 ml) before the age of 9 years in boys, as a result of the early activation of the hypothalamic-pituitary-gonadal axis.
- Activation of hypothalamic Gonadotropin-Releasing Hormone (GnRH) pulse generator increases Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) secretion and release of sex steroids with normal-sequence pubertal development.
- It occurs 5–10 fold more frequently in girls than in boys.
- Approximately 90% of girls have an idiopathic form.
- A structural Central Nervous System (CNS) abnormality can be found in up to 75% of boys with central precocious puberty.
- Central precocious puberty can impact linear growth and affect the child's growth potential.

Clinical findings

- Female central precocious puberty commonly starts with breast development, followed by pubic hair growth and menarche. But, this order may vary.
- Girls with ovarian cysts or tumors presents with signs of estrogen excess such as breast development and vaginal bleeding.
- Adrenal tumors or congenital adrenal hyperplasia presents with signs of adrenarche (i.e. pubic hair, axillary hair, acne, and increased body odor).
- Children with precocious puberty initially have accelerated growth (tall for age). However, as skeletal maturation advances at a more rapid rate than linear growth, final adult height may be compromised (short stature).

Diagnosis

- Radiograph of the left hand and wrist to determine skeletal maturity (bone age). Further evaluation is needed, if the bone age is advanced.
- Measurement of LH and FSH levels.
- GnRH agonist (leuprolide) stimulation test:
    - In central precocious puberty, basal LH and FSH levels are not in pubertal range. LH response to GnRH is pubertal.
- In girls with an ovarian cyst or tumor, estradiol levels are raised.
- In girls with signs of adrenarche and an advanced bone age, androgen levels (testosterone, androstenedione, dehydroepiandrosterone) and adrenal intermediate *metabolites (such as 17-hydroxyprogesterone) should* be measured.
- Elevated testosterone levels in boys verify early pubertal status but do not differentiate the source.
- For central precocious puberty an MRI of the brain should be done to evaluate for CNS lesions.
- For peripheral precocious puberty in girls, an ultrasound of the ovaries and adrenal gland is indicated.
- Ultrasonography in boys may be useful in detecting hepatic, adrenal, and testicular tumors causing precocious puberty.
- Serum β-HCG concentrations show the presence of an HCG-producing tumor (e.g. CNS dysgerminoma or hepatoma) in boys.

Management

- Girls with central precocious puberty can be treated with GnRH analogues, such as leuprolide. GnRH analogues down regulate pituitary GnRH receptors and thus decrease gonadotropin secretion.
- Treatment of peripheral precocious puberty is dependent on the underlying cause.
- In a girl with an ovarian cyst, treatment is generally not necessary, as the cyst usually regresses spontaneously.
- Treatment with glucocorticoids is indicated for congenital adrenal hyperplasia.
- Surgical resection is indicated for the rare adrenal or ovarian tumor.
- In McCune-Albright syndrome, therapy contains:
    - Antiestrogens (e.g. tamoxifen)
    - Agents that block estrogen synthesis (ketoconazole)
    - Aromatase inhibitors (e.g. letrozole)
- Attention to the psychological needs of the patient and family is essential.

Incomplete (partial) precocious development

- Partial precocious puberty means isolated manifestations of precocity without development of other signs of puberty.
- Development of the breasts in girls and growth of sexual hair in both sexes are the two most common forms.

Premature thelarche

CASE

A 2-year-old girl presents with right-sided ***breast enlargement***. She is ***otherwise normal***. There are no other signs and symptoms of pubertal development.

- This is a transient condition of isolated breast development that most often appears in the first 2 years of life.
- It may be unilateral or asymmetric.

- Other signs of pubertal development (accelerated growth rate or skeletal maturation, pubic hair, vaginal mucosal maturation) are absent.
- Osseous maturation is normal or slightly advanced.
- The genitalia show no evidence of estrogenic stimulation.
- Breast development may regress after 2 yr, often persists for 3–5 yr, and is rarely progressive.
- Menarche occurs at the expected age, and reproduction is normal.
- In the absence of other signs of pubertal development no laboratory evaluation is necessary.
- Premature thelarche is a benign condition but continued observation is important because the condition cannot be readily distinguished from true precocious puberty (especially in children older than 3 years of age).

Premature pubarche (adrenarche)

CASE

A 6-year-old girl presents with history of ***pubic and axillary hair development*** for the last 5 months. There is ***no history of menstruation***. On examination, she is on the 80th centile for height and weight. There is ***no breast development***.

- Premature adrenarche (benign early adrenal maturation) is manifested by development of pubic hair and body odor, and less commonly, axillary hair and can occur before age 8 years.
- It is much more frequent in girls than in boys.
- There is no increase in growth rate or skeletal maturation.
- There is no abnormal virilization (e.g. clitoromegaly).
- No treatment is required, although girls with premature adrenarche are at risk for developing polycystic ovarian syndrome during puberty.

Premature menarche

- This is a diagnosis of exclusion.
- This is a condition of girls, with isolated vaginal bleeding in the absence of other secondary sexual characteristics.
- First of all, other causes of vaginal bleeding are excluded (e.g. vulvovaginitis, a foreign body, sexual abuse, and urethral prolapsed, etc.).
- The majority of girls with idiopathic premature menarche have only 1–3 episodes of bleeding.
- Puberty occurs at the usual time.
- Menstrual cycles are normal.

DELAYED PUBERTY

CASE

Familial delayed puberty: 14-year-old girl has ***not yet started her periods***. She is ***developmentally normal***. On examination, she is ***pre-pubertal***.

DELAYED PUBERTY IN GIRLS

- Puberty is diagnosed as delayed, if there is absence of pubertal signs by 13 years or menarche by 16 years in girls.
- There is failure to complete Tanner stage V of puberty within 4 years of onset.

Causes

- Primary hypogonadism:
    - Turner syndrome or other gonadal dysgenesis
    - Ovarian failure due to autoimmune disease
    - Surgery
    - Radiation
    - Chemotherapy
    - Galactosemia
- Central hypogonadism:
    - Pituitary or hypothalamic tumors
    - Congenital hypopituitarism
    - Kallmann syndrome
    - Chronic illness
    - Undernutrition
    - Excess exercise
    - Hyperprolactinemia
- Anatomic:
    - Mullerian agenesis
    - Complete androgen resistance

Diagnosis

- Primary ovarian failure causes elevated FSH (Turner syndrome)
- Central hypogonadism causes low gonadotropin

Differential diagnosis

- Constitutional growth delay
- Secondary amenorrhea (weight loss, medication, chronic intercurrent illness)
- Hypothyroidism and GH deficiency
- Absence of the uterus (androgen insensitivity)
- Polycystic ovarian syndrome (failure to menstruate with normal estrogen)
- Anorexia nervosa (in the underweight teenage girl with secondary amenorrhea)

Management

- Replacement therapy in hypogonadism:
    - Start with estrogen followed in 12–18 months with cyclic estrogen-progesterone therapy.
- Treat the primary cause.

DELAYED PUBERTY IN BOYS

- Puberty is diagnosed delayed if there is lack of secondary sexual characteristics by age 14 years in boys.

Causes

- Primary testicular failure:
  - Testicular absence or hypoplasia (Klinefelter syndrome is the most common cause)
  - Destruction of testes by irradiation
  - Infection (mumps)
  - Autoimmune inflammation
  - Trauma or tumor
  - Enzyme defects
- Secondary testicular failure:
  - Pituitary or hypothalamic disease
  - Isolated LH or FSH deficiency due to GnRH deficiency (Prader-Willi and Laurence-Moon syndrome)
  - Destructive brain tumors or infections
  - Chronic debility
  - Hypothyroidism

Diagnosis

- Primary testicular failure:
  - Low plasma testosterone with elevated LH and FSH.
- Secondary testicular failure:
  - Testosterone, LH, and FSH are below normal.
- Presence of testes and their ability to respond is measured by plasma testosterone after intramuscular hCG.

Differential diagnosis

- Constitutional growth delay (most common cause of delayed puberty. There is normal growth velocity and delayed bone age).
- Masculinized female (in such a case check karyotype and look for adrenal hyperplasia).
- Cryptorchidism (this may be an isolated finding or associated with hypothalamic-pituitary-gonadal axis, androgen synthesis or receptor defects).
- Abdominal testes (in this case, plasma testosterone after hCG stimulation will be normal).

Management

- Specific therapy depends on cause. Constitutional delay may respond to short course (4–6 months) of low-dose depot testosterone (50–70 mg/month) to stimulate their pubertal appearance and enhance to start their endogenous development.
- Permanent hypogonadism requires regular depot testosterone (50–70 mg up to 150–200 mg/2–3 months) given until their growth is complete.

HYPOTHYROIDISM

- Thyroid hormone is critical for normal postnatal somatic growth and neurologic development in infants and children.
- Deficiency of thyroid hormone in first 2 years of life may result in severe psychomotor retardation.
- Thyroid hormone is also necessary for skeletal growth and maturation in growing children.
- It plays a major role in oxidative metabolism and heat production.
- Hypothyroidism may occur at birth (congenital hypothyroidism) or at any time during childhood or adolescence (juvenile hypothyroidism).

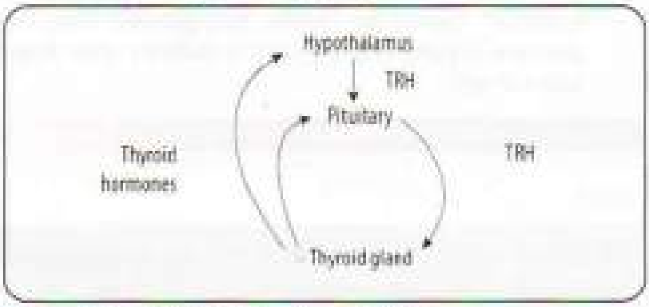


Figure 19.3: Thyroid hormone regulation.

CONGENITAL HYPOTHYROIDISM

CASE

A 2-week-old boy presents with ***constipation*** and ***jaundice***. He is sluggish (hypotonia) and excessive sleepy. On physical examination, he has mild jaundice with a distended abdomen. He has a ***large tongue***, a ***large anterior and posterior fontanel***, an ***umbilical hernia***, and a coarse dry skin. Plasma T_4 is decreased and TSH is raised. No ossification center at knee X-ray. Isotope and ultrasound scanning showed no thyroid tissue.

- Most cases of congenital hypothyroidism are not hereditary and result from thyroid dysgenesis.

Definition

- Congenital hypothyroidism is defined as a significant decrease in, or the absence of, thyroid function present at birth.

INCIDENCE

- Congenital hypothyroidism affects boys and girls equally.
- Worldwide 1:4000 infants are affected.
- Goitrous congenital hypothyroidism occurs in about 1:30,000 live births and reflects inborn defect in hormone synthesis or effect, or transplacental passage of anti-thyroid drugs.

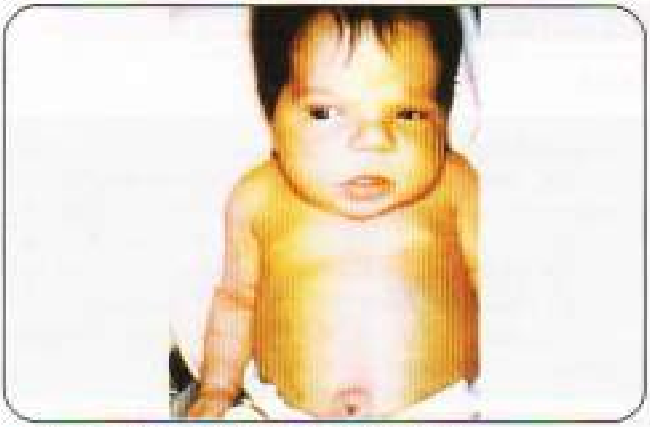


Figure 19.4 (A): Congenital hypothyroidism.

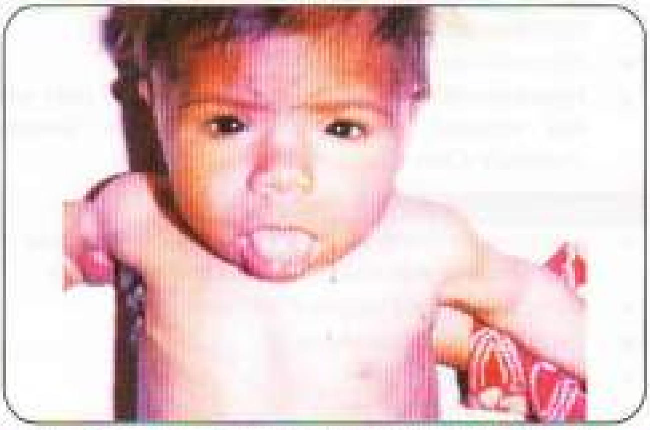


Figure 19.4 (B): Congenital hypothyroidism. Note coarse facies and large tongue.

Etiology

- Dysgenesis or aplasia of thyroid gland (90% of cases)
- Ectopic thyroid gland
- Inborn defect of thyroxine synthesis (may involve defects of iodine transport, organification, thyroglobulin synthesis, or deiodination)
- End organ resistance to thyroxine
- Hypothalamic-pituitary-thyroid axis defect (TRH or TSH deficiency)
- Endemic goiter (iodine deficiency)
- Transplacental suppression of thyroid by drugs, antibodies, etc.
- Idiopathic

Clinical findings

- Because thyroid hormone does not appear to be necessary for fetal growth, infants with congenital hypothyroidism are normal at birth and gain weight normally, even if untreated, for the first 3–4 months of life.
- The severity of symptoms and physical findings correlates with the degree of hypothyroidism.
- At birth, gestation may be >42 weeks (50%), and birth weight >4 kg (25%).
- After birth, there may be:
    - Hypothermia
    - Acrocyanosis
    - Respiratory distress
    - Large posterior fontanel
    - Bradycardia
    - Poor muscle tone
    - Poor feeding
    - Prolonged neonatal jaundice (75%)
- Other symptoms that may be apparent after the first 1–2 months of life are:
    - Feeding problems
    - Lethargy
    - Constipation
    - Noisy breathing
    - Abdominal distension
    - Umbilical hernia
    - Mottled dry skin
    - Coarse facies
    - Large tongue
    - Thick lips
    - Large open fontanels
    - Hypotonia
    - Hoarse cry
    - Scanty dry and brittle scalp hair
    - Lateral thinning of eye brows
    - Non-pitting edema
    - Anemia
    - A slow relaxation component of deep tendon reflexes is present (best appreciated in the ankle)
- Severe congenital hypothyroidism is characterized by:
    - Short stature
    - Epiphyseal dysgenesis
    - Impaired physical growth and development
    - Mental retardation

Diagnosis

- **Linear growth:**
    - There is short stature
    - Ratio of upper to lower segment is abnormal (infantile)
- **Thyroid function test:**
    - Decreased serum concentration of total T_4
    - Elevated serum concentrations of TSH
- **X-rays:**
    - Retardation of osseous development. At birth, there is no epiphysialcenter visible at knee joint.
    - In older children, the epiphysis often has multiple foci of ossification (epiphyseal dysgenesis).
    - Bone age is delayed.
    - X-ray skull shows large fontanel and wide sutures and intersutural bones (wormian bones).
- **Thyroid scan:**
    - It differentiates between agenesis and ectopic thyroid.

- It includes ultrasound scan, technetium scan, or iodine uptake and perchlorate discharge test.
- A technetium scan shows:
  - Absence of ^{99m}Tc uptake indicates thyroid agenesis.
  - Increased ^{99m}Tc uptake in a normally positioned gland shows an enzymatic defect in thyroid hormone production.
  - An ectopic gland is demonstrated by abnormal localization of ^{99m}Tc uptake.

- **ECG:**
  - Low-voltage P and T waves with diminished amplitude of QRS complexes and suggest poor left ventricular function and pericardial effusion.
- **EEG:**
  - It shows low voltage.

Treatment

- Lifelong treatment with **thyroid hormone replacement**.
- Thyroxin is given as a single daily oral dose.
- Dose is 10–15 mg/kg/day in neonates, and 4 □g/kg/day in children.
- As the child grows, the dosage is adjusted to maintain the serum T_4 in the high-normal range.
- Adequate dose is indicated by alertness and increase in activity, appetite, skin becoming warm and smooth, improvement of constipation and normal linear growth.
- Over dose is indicated by diarrhea, restlessness, excitability, sleeplessness, tachycardia, hyperthermia, and tremors.

Follow up

- Growth and neurologic development are evaluated by regular follow up every 2–3 months in the first 2 years of age, with somewhat less frequent follow up after 2 years of age.
- In follow up visits, weight, height, bone age and developmental assessment is done.

Prognosis

- When diagnosed and treated within the first few weeks of life, there is normal growth and intelligence.
- When the diagnosis of congenital hypothyroidism is delayed beyond 6 months of age, a high proportion of children suffer permanent neurologic impairment.

Neonatal screening

- Congenital hypothyroidism in the next pregnancy should be diagnosed by neonatal screening within 10 days of birth.

JUVENILE (ACQUIRED) HYPOTHYROIDISM

CASE

Acquired hypothyroidism: A 9-year-old girl has ***short stature***, and ***slow growth***. She is ***overweight*** and ***lethargic***. She complains of ***cold intolerance***. She is pale. Her growth curve demonstrates that she has fallen from the 50th percentile to the 5th percentile for height. Her weight has increased to the 90th percentile. On examination, she has ***slow reflexes***. ***Bone age*** is ***delayed*** on X-ray.

Definition

- When symptoms appear after first year of life, hypothyroidism is presumed to be acquired.
- It is more common in girls than in boys.
- Hypothyroidism should be suspected in any child who has retarded growth or slow growth velocity, especially if not associated with weight loss.

Etiology

- Lymphocytic thyroiditis (autoimmune destruction or Hashimoto thyroiditis) is the most common cause.
- Defects in thyroid hormone synthesis
- Ectopic thyroid dysgenesis
- Thyroidectomy
- Removal of ectopic tissue
- Irradiation
- Ingestion of iodide containing medications
- Idiopathic

Clinical features

- Growth retardation
- Skin changes
- Constipation
- Cold intolerance
- Less energy
- Increased sleep
- Delayed bone age
- Some children may present with headache, visual problems, precocious puberty, or galactorrhea.
- These manifestations return to normal with treatment.
- With long standing hypothyroidism, adult height may be impaired.

Diagnosis

- Decreased serum concentrations of total T_4
- Elevated serum concentrations of TSH
- Delayed bone age on X-ray
- Presence of circulating thyroid antibodies shows autoimmune basis of the disease

Treatment

- Thyroid hormone replacement therapy (thyroxine)

Prognosis

- Acquired hypothyroidism is not a cause of permanent developmental delay.
- Unless hypothyroidism develops around the time of puberty when skeletal maturation is nearly complete, the prognosis for catch-up growth is good. Some children may not reach their genetic potential for growth.
- Other signs and symptoms improve completely.
- Children with autoimmune hypothyroidism are at increased risk for other associated autoimmune diseases, such as diabetes mellitus and adrenal insufficiency.

THYROIDITIS

CHRONIC LYMPHOCYTIC THYROIDITIS

- Also called Hashimoto thyroiditis or autoimmune thyroiditis.
- There is firm, freely movable, nontender, diffusely enlarged thyroid gland.
- Thyroid function is usually normal but may be elevated or decreased depending on the stage of the disease.

Clinical findings

- It is the most common cause of goiter and hypothyroidism in children.
- Female/Male ratio is 4:1.
- This is a autoimmune-mediated disorder.
- Usual presentation is as hypothyroid symptoms, goiter, positiveantithyroid peroxidase antibodies. May present with hyperthyroid symptoms
- TSH is generally normal. TSH low during hyperthyroid phase of thyrotoxicosis. TSH is high during hypothyroid phase of thyroiditis.
- This disorder may be associated with autoimmune polyglandular syndrome type 2 (adrenal failure, autoimmune thyroid disease, type 1 diabetes mellitus, vitiligo, celiac disease, atrophic gastritis, gonadal failure).

Differential diagnosis

- Idiopathic goiter
- Graves disease
- Viral thyroiditis
- Iodine deficiency
- Goitrogen ingestion
- Congenital hypothyroidism

Management

- Ideal treatment has not been established.
- Exogenous thyroid hormones are given which decreases goiter size but does not prevent progression of disease
- Regular monitoring for the development of hypothyroidism or Graves disease is needed.

HYPERTHYROIDISM

CASE

A 12-year-old girl presents with a three months history of ***heat intolerance***, ***weight loss*** and poor concentration. On examination, there is symmetrical smooth ***goiter***, ***proptosis*** and ***tachycardia***. Investigations show ***TSH suppression*** with ***high free T_4 and T_3***.

- Hyperthyroidism results from excessive secretion of thyroid hormone.
- During childhood, with few exceptions, it is caused by Graves disease.
- **Graves disease** is an autoimmune disorder.

GRAVES DISEASE

Etiology

- Graves disease (diffuse toxic goiter):
  - It is hyperthyroidism secondary to diffuse thyroid hyperplasia.
  - It is an autoimmune disorder. Enlargement and hyperfunction of the thyroid gland is stimulated by circulating immunoglobulins. Stimulatory immunoglobulins lead to increased levels of free T_4 that suppresses TSH to undetected levels.
- Neonatal Graves disease:
  - It is caused by transplacental passage of thyroid-stimulating immunoglobulins (i.e. IgG).
- Autonomous hyperfunctioning hot thyroid nodule
- Subacute thyroiditis

Clinical findings

- Girls are more commonly affected than boys (ratio 5:1).
- There is often a family history of Graves disease.
- The usual age of manifestation is after 5 years of age.
- The onset of symptoms is insidious.
  - Emotional liability
  - Increased appetite
  - Heat intolerance
  - Weight loss
  - Frequent loose stools
  - Deterioration of behavior and school performance
  - Poor sleeping
- Child appears flushed and warm.
- There is marked tachycardia, fever, diaphoresis, nausea and vomiting (thyroid storm).
- There may be proptosis and widened palpebral fissures.
- Thyroid gland is diffusely enlarged, smooth, firm, but not hard. It is nontender.
- Precordium is hyperactive. There is resting tachycardia and widened pulse pressure.

- Skin is smooth, warm, flushed, and moist.
- There may be a fine tremor of outstretched fingers, and proximal muscle weakness.

Diagnosis

- Increased serum concentrations of total T_4 (or free T_4) and total T_3
- Low or suppressed levels of TSH
- Increased radioactive iodine uptake

Management

- Antithyroid medications:
  - Propylthiouracil (PTU) 150–600 mg/day
  - Methimazole 15–60 mg/day
- Propranolol 10–20 mg four times daily for 2–4 weeks may give symptomatic relief.
- Subtotal thyroidectomy is indicated if the patient is noncompliant with medical therapy.
- Radioactive iodine is used for ablation of thyroid tissue.

CONGENITAL HYPERTHYROIDISM

CASE

A 5-days old full term 3.2 kg neonate presents with irritability, ***jitteriness***, ***tachycardia***, ***sweating***. He has difficulty to feed and ***diarrhea***. Heart rate is 190 beats/minute (*tachycardia*). Respiratory rate is 80 breaths/minute (*tachypnea*). Liver is 4 cm palpable. He has poor peripheral pulses. His mother is getting treatment for hyperthyroidism.

- Transient congenital hyperthyroidism or neonatal Graves disease occurs in about 1% of infants born to mothers with Graves disease.
- It occurs when maternal TSH receptor antibodies cross the placenta and stimulate excess thyroid hormone production in the fetus and newborn.

Clinical findings

- Irritability, IUGR, poor weight gain, flushing, jaundice, hepatosplenomegaly, and thrombocytopenia.
- Severe cases may result in cardiac failure and death.
- Hyperthyroidism may develop several days after birth, especially if the mother was treated with PTU which crosses the placenta. Symptoms develop as PTU levels decline in the newborn after birth.

Diagnosis

- Thyroid studies are obtained at birth and repeated within the first week.

Management

- Immediate management of cardiac manifestations is needed.
- Temporary treatment may be necessary with iodide, antithyroid agents, -adrenergic antagonists, or corticosteroids.
  - Oral propranolol (1–2 mg/kg/24 hours, orally in 3 divided doses)
  - Methimazole (0.25–1.0 mg/kg/24 hours given every 12 hours)
  - Saturated solution of potassium iodide (1 drop per day) may be added)
- If heart failure occurs, digitalization is indicated.
- Hyperthyroidism gradually resolves over 1–3 months as maternal antibodies decline.

HYPOPARATHYROIDISM

CASE

A 2-year-old male child presents with generalized tonic-clonic afebrile convulsive attack. Cerebrospinal fluid examination and EEG are normal. Serum calcium, Vitamin D_3, and PTH levels are low.

Clinical findings

- Hypocalcemia causes tetany: muscular pain, cramps, numbness, stiffness, tingling of the hands and feet, positive Chvostek or Trousseau sign or laryngeal and carpopedal spasms, convulsions.
- Headache, vomiting, increased ICP, papilledema–may suggest a brain tumor.
- In long standing hypocalcemia–teeth erupt late and irregularly–enamel formation is irregular–skin may be dry and scaly–nails may have horizontal lines.
- Mucocutaneous candidiasis
- Cataracts

Diagnosis

- Serum calcium level is low (Ca 5–7 mg/dL)
- Serum phosphorus elevated (7–12 mg/dL)
- Alkaline phosphatase (normal or low)
- 1, 25 $(OH)_2$ D_3 (usually low)
- Magnesium (normal)
- PTH levels (low)
- Radiographs or CT scans of the skull (calcifications in the basal ganglia)
- ECG (prolongation of the QT interval)
- EEG (shows widespread slow activity)

Differential diagnosis

- Pseudo-hypoparathyroidism
- Transient tetany in newborns is a relative Parathyroid Hormone(PTH) deficiency associated with high phosphate diet (whole cow's milk), infant of diabetic mother, fetal alcohol syndrome.
- Severe vitamin D deficiency

- Gastrointestinal (GI) malabsorption syndromes, chronic renal disease, tumorlysis syndrome, rhabdomyolysis
- DiGeorge syndrome—congenital absence of parathyroid gland
- Autoimmune polyendocrine syndrome type 1
- Autosomal dominant hypocalcemia—gain of function mutation in extracellular calcium receptor which causes low serum PTH despite calcium loss and hypocalcemia
- Postoperative or postradiation for thyroid disease
- Iron or copper overload—hemochromatosis, thalassemia, Wilson's disease
- Hyperandhypomagnesemia

Management

- Treatmentof severe tetany or seizures resulting from hypocalcemia is intravenous calcium gluconate (1 to 2 ml/kg of a 10% solution) given slowly over 10 minutes under cardiac monitoring (ECG for bradycardia, which can be fatal).
- Long-term treatment of hypoparathyroidism involves administering vitamin D, preferably as 1,25-dihydroxyvitamin D and calcium.
- Therapy is adjusted to keep the serum calcium in the lower half of the normal range to avoid episodes of hypercalcemia that might produce nephrocalcinosis and to avoid pancreatitis.
- High calcium diet and dietary calcium supplements
- Vitamin D supplementation with calcitriol
- Treat underlying cause if possible
- PTH is not generally used

PSEUDO-HYPOPARATHYROIDISM

(Albright Hereditary Ostrodystrophy)

- PTH elevated even when the patient is hypocalcemic or normocalcemic.
- Biochemical features of pseudo-hypoparathyroidism are similar to those of hypoparathyroidism with the one exception that in pseudo-hypoparathyroidism, PTH levels are elevated.

Clinical findings

- Tetany
- Short stature
- Round face
- Obesity
- Dental hypoplasia
- Brachydactyly (index finger may be longer than middle finger; usually due to shortened fourth or fifth metacarpals or metatarsals)
- Short and wide phalanges, bowing exostoses, and thickening of the calvaria
- Calcium deposits and metaplastic bone formation subcutaneously (subcutaneous calcifications)
- Mental retardation (below normal IQ)
- Calcification of basal ganglia
- Lenticular cataracts
- Other hormone abnormalities (hypothyroidism, hypogonadism)

Diagnosis

- Hypocalcemia
- Hyperphosphatemia
- Elevated PTH levels
- Alkaline phosphatase (increased)

Management

- Same as for hypoparathyroidism
- Specific treatment is needed for ocular, mental, and physical disabilities

HYPERPARATHYROIDISM

CASE

A 6-year-old child presents with complaint of ***numbness and tingling of the hands***. He also has history of tonic clonic***seizures***. Laboratory investigations show ***low PO4*** and ***high Ca^{++}***

Clinical findings

- Muscular weakness, fatigue, headache, anorexia, abdominal pain, nausea, vomiting, constipation, polydipsia, polyuria, loss of weight, fever
- Nephrocalcinosis
- Progressively diminished renal function (renal calculi–renal colic–hematuria).
- Osseous changes may produce pain in the back or extremities, disturbances of gait, genu valgum, fractures, and tumors.

Diagnosis

- Serum calcium level is elevated (>12 mg/dL)
- Serum phosphorus level is reduced (<3 mg/dL)
- Serum magnesium–low
- Urine may have a low and fixed specific gravity
- Serum levels of PTH–elevated
- Radiographic findings–resorption of subperiosteal bone

Differential diagnosis

- Other causes of hypercalcemia can result in a similar clinical pattern and must be differentiated from hyperparathyroidism:
    - Excessive Calcium or Vitamin D
    - Hypercalcemia of malignancy (Primary bone tumors, Metastatic tumors with osteolysis)
    - Endocrinopathies: Hyperthyroidism, Addison disease, Pheochromocytoma
    - Acute or Chronic Renal Failure
    - Hypophosphatasia

Management

- Surgical exploration is indicated in all patients.
- If an adenoma is discovered, it should be removed.
- Most neonates with severe hypercalcemia require total parathyroidectomy.
- A portion of a parathyroid gland may be auto-grafted into the forearm.

Prognosis

- If the disease is recognized early and there is appropriate surgical treatment, then prognosis is good.
- Deformities are permanent, when extensive osseous lesions are present.

ADDISON DISEASE

CASE

A 6-year-old child presents with tiredness and weight loss for few weeks. There is blackening of skin color due to ***generalized pigmentation***. On laboratory investigations, Na^+ 118 (***hyponatremia***), K^+ 7.5 (***hyperkalemia***) ACTH and rennin levels are raised.

- Acquired primary adrenal insufficiency (originating in the gland itself) → termed Addison disease.
- In primary adrenal insufficiency, congenital or acquired lesions of the adrenal cortex prevent production of cortisol and often aldosterone.
- Dysfunction of the hypothalamus or anterior pituitary gland cause a deficiency of corticotropin (ACTH) lead to hypofunction of the adrenal cortex, termed secondary adrenal insufficiency.

Causes

Primary adrenal insufficiency

- Congenital adrenal hyperplasia
- Adrenoleukodystrophy
- Adrenal Hypoplasia Congenita
- Autoimmune Addison disease
- Infections (tuberculousadrenalitis, meningococcal sepsis or Waterhouse-Friderichsen syndrome, fungal adrenalitis)
- Bilateral adrenal hemorrhage
- Bilateral adrenal metastases
- Bilateral adrenalectomy

Secondary adrenal insufficiency

- Drug induced (e.g. ketoconazole)
- Abrupt cessation of glucocorticoid therapy (systemic or topical)
- Hypothalamic or pituitary tumors
- Hypothalamic or pituitary surgery or irradiation
- Prader-Willi syndrome

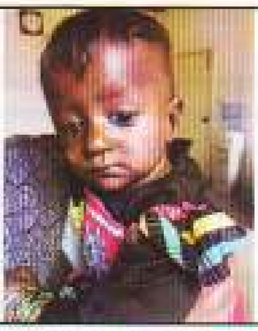
Clinical findings

Due to cortisol deficiency

- Hypoglycemia (Hypoglycemia is a prominent feature of adrenal insufficiency. It is often accompanied by ketosis as the body attempts to utilize fatty acids as an alternative energy source.)
- Inability to withstand stress
- Hypotension or decreased cardiac output (shock).
- Muscle weakness, fatigue.
- Hyperpigmentation due to increased ACTH.

Due to aldosterone deficiency

- Hyponatremia • Hyperkalemia • Vomiting
- Urinary sodium wasting • Salt craving • Acidosis
- Failure to thrive • Volume depletion • Hypotension
- Dehydration • Shock • Diarrhea
- Muscle weakness



Blackening of skin in Addison disease

Diagnosis

- Hypoglycemia • Ketosis • Hyponatremia
- Hyperkalemia • Acidosis
- Blood urea nitrogen (increased)
- Urinary excretion of sodium and chloride are increased and urinary potassium is decreased.
- **ACTH (cosyntropin) stimulation test:** The **most definitive test for adrenal insufficiency** is measurement of serum levels of cortisol before and after administration of ACTH.
  - Resting levels are low and do not increase normally after administration of ACTH may indicate primary adrenal insufficiency.
  - A low initial level followed by a significant response to ACTH may indicate secondary adrenal insufficiency.
  - Traditionally, this test has been performed by measuring cortisol levels before and 30 or 60 minutes after giving 0.250 mg of cosyntropin (ACTH 1–24) by rapid intravenous infusion.
- Baseline serum ACTH concentration: Values are elevated in primary adrenal failure and low in central adrenal insufficiency.
- Urinary free cortisol and 17-hydroxycorticosteroid excretion: Values are decreased.

- CRH test: This test assesses responsiveness of the entire hypothalamic-pituitary-adrenal axis. After administration of ovine CRH, serum concentrations of ACTH and cortisol are measured over 2 hours.
- Ultrasonography, CT, or MRI may help define the size of the adrenal glands.

Differential diagnosis

- Gastroenteritis with dehydration
- Sepsis
- Diabetic coma
- When congenital adrenal hyperplasia is suspected, serum levels of cortisol precursors (17-hydroxyprogesterone) should be measured along with cortisol in an ACTH stimulation test.
- Adrenoleukodystrophy. Elevated levels of very long chain fatty acids are diagnostic of adrenoleukodystrophy
- Adrenal tumor, calcification, and hemorrhage (Waterhouse-Friderichsen)
- Adrenal tuberculous or fungal infections (especially in immunodeficiency). The presence of anti-adrenal antibodies suggests an autoimmune pathogenesis. Patients with autoimmune Addison disease must be closely observed for the development of other autoimmune disorders
- Anterior pituitary tumor
- Temporary salt losing due to mineralocorticoid deficiency or renal under-responsiveness (pseudo-hypoaldosteronism) in infants with pyelonephritis.
- Septic shock, diabetic coma, CNS diseases, and acute poisoning mimic adrenal crisis.

Management

- Treatment must be immediate and vigorous.
- A blood sample must be obtained before therapy for determination of electrolytes, glucose, ACTH, cortisol, aldosterone, and plasma rennin activity.
- IV administration of 5% glucose in 0.9% saline solution to correct hypoglycemia, hypovolemia, and hyponatremia.
- If hyperkalemia is severe, it may require treatment with:
  - Intravenous calcium and/or bicarbonate
  - Intra-rectal potassium binding resin (kayexalate)
  - IV infusion of glucose and insulin
- Hydrocortisone sodium succinate (glucocorticoid): Hydrocortisone sodium succinate is given initially at a dose of 50 mg/m^2 intravenously over 2–5 minutes or intramuscularly; thereafter, it is given intravenously, 12.5 mg/m^2, every 4–6 hours until stabilization is achieved and oral therapy can be tolerated.
- Fludrocortisone (mineralocorticoid): When oral intake is tolerated, fludrocortisone, 0.05–0.15 mg daily, is started and continued as necessary every 12–24 hours for primary adrenal insufficiency.
- ACTH levels may be used to monitor adequacy of glucocorticoid replacement.
- During situations of stress, infection, operation, the dose of hydrocortisone should be increased 2–3 fold.
- Additional therapy may be needed to be directed at the underlying cause of the adrenal insufficiency in regard to infections and certain metabolic defects.
- Therapeutic approaches to adrenoleukodystrophy include administration of glycerol trioleate and glycerol trierucate (Lorenzo's oil), bone marrow transplantation, and lovastatin.
- Secondary adrenal insufficiency most commonly occurs when the hypothalamic-pituitary-adrenal axis is suppressed by prolonged administration of high doses of a potent glucocorticoid and that agent is suddenly withdrawn or the dose is tapered too quickly.
  - When a patient is thought to be at risk, tapering the dose rapidly to a level equivalent to or slightly less than physiologic replacement (~10 mg/M^2/24 hours of hydrocortisone) and further tapering over several weeks may allow the adrenal cortex to recover without development of signs of adrenal insufficiency.

Maintenance therapy

- Following initial stabilization, the most effective substitution therapy is hydrocortisone, combined with fludrocortisone in primary adrenal insufficiency.
- Glucocorticoids: A maintenance dosage of 6–10 mg/m^2/d of hydrocortisone (or equivalent) is given orally in two or three divided doses. The dosage of all glucocorticoids is increased to 30–50 mg/m^2/d during intercurrent illnesses or other times of stress.
- Mineralocorticoids: In primary adrenal insufficiency, fludrocortisone is given, 0.05–0.15 mg orally daily as a single dose or in two divided doses. Periodic monitoring of blood pressure is recommended to avoid overdosing.
- Salt: The child should be given ready access to table salt.

Prognosis

- The course of acute adrenal insufficiency is rapid, and death may occur within a few hours, particularly in infants, unless adequate treatment is given. Spontaneous recovery is unlikely.
- Patients with chronic adrenocortical insufficiency who get adequate therapy may have normal lives.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

CASE

Salt-losing congenital adrenal hyperplasia (21-hydroxylase deficiency): A 9-day-old boy presents with ***vomiting*** and ***dehydration***. Physical examination is otherwise normal. But there is ***ambiguous genitalia*** and minimal hyperpigmentation of the nipples. On laboratory investigations, serum sodium and potassium concentrations are 120 mEq/L and 9 mEq/L, respectively (***hyponatremia, hyperkalemia***). A serum 17-hydroxyprogesterone level is elevated.

- This autosomal recessive disorder causing mutations in the enzymes of adrenal steroidogenesis in the fetus.
- This causes abnormal cortisol biosynthesis with increased ACTH secretion.
- Its incidence is 1–15/20,000 births with 70% salt losing form and 30% with virilizing form.

Pathogenesis

- ACTH excess subsequently results in adrenal hyperplasia with increased production of adrenal hormone precursors, including androgens.
- Increased pigmentation, especially of the scrotum, labia majora, and nipples, is common with excessive ACTH secretion.
- 90% of cases of CAH are due to deficiency of 21-∝ hydroxylase enzyme required for cortisol and aldosterone biosynthesis, and 5% of cases being associated with a deficiency of the 11-b-hydroxylase enzyme.
- Signs and symptoms of each enzymatic disorder depend on the deficient or in excess hormone.
- Increased androgen production may cause:
  - Female pseudo-hermaphroditism by affecting the development of the female genitalia in utero
  - Virilization in childhood with phallic enlargement in either sex, development of pubic hair, or a rapid growth rate
  - Milder virilization in females at or after puberty, with amenorrhea
- Aldosterone synthesis may be markedly reduced in more than 50% of the infants with 21-∝-hydroxylase deficiency and may cause an Addisonian-like picture with marked renal sodium loss during the first few weeks of life. There is severe vomiting. Hyponatremia and hyperkalemia is due to volume depletion.

Clinical findings

- The newborn presents with vomiting, dehydration, weight loss hypoglycemia, hyponatremia and hyperkalemia at 10–14 days of age.

In females: (there is ambiguous genitalia)

- Abnormality of the external genitalia (varies from enlargement of the clitoris resembling a penis with complete fusion of the labioscrotal folds).
- Signs of adrenal insufficiency (salt loss) typically appear in the first or second week.
- Rarely, adrenal insufficiency does not occur for months or years. With milder enzyme defects, salt loss may not occur, and simple virilization predominates.

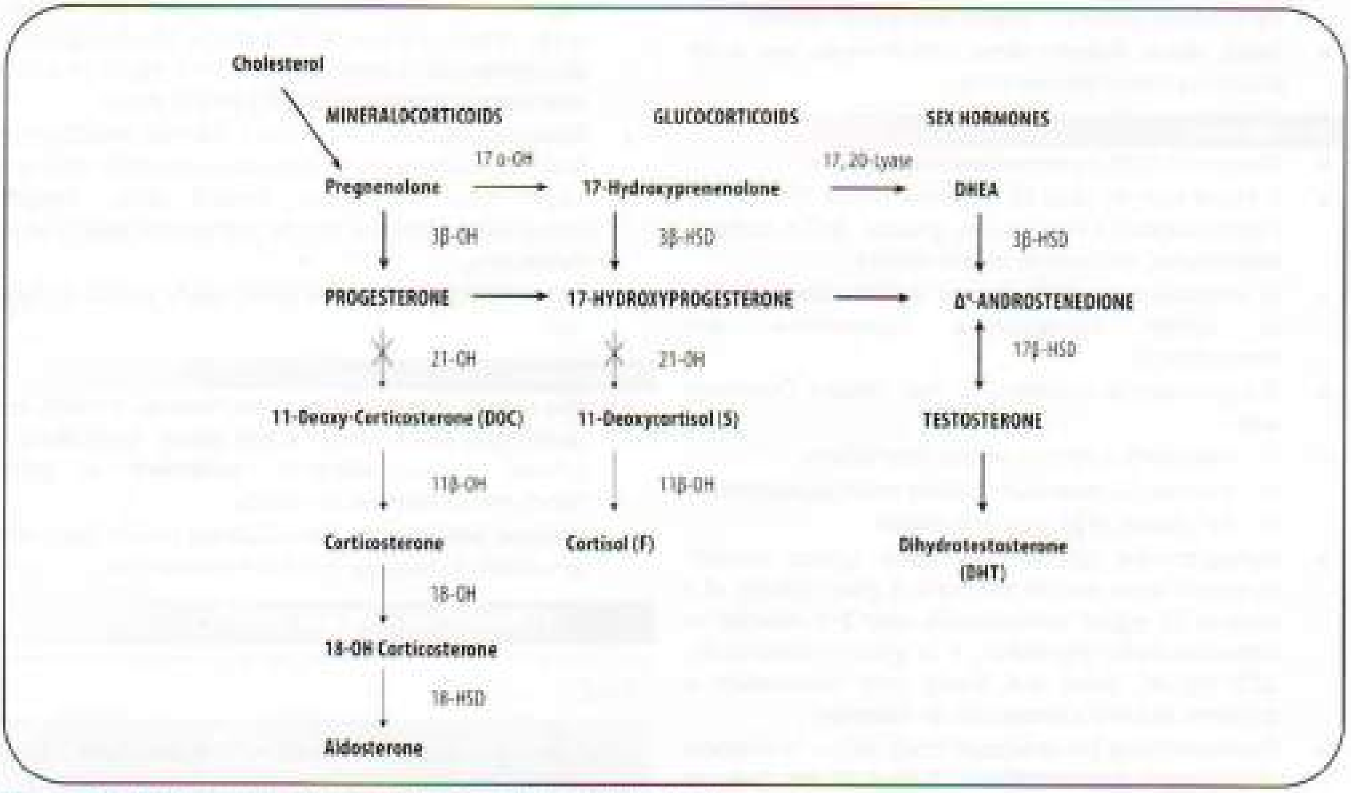

Cholesterol
MINERALOCORTICOIDS
GLUCOCORTICOIDS
SEX HORMONES
17 α-OH
17, 20-Lyase
Pregnenolone
17-Hydroxyprenenolone
DHEA
3β-OH
3β-HSD
3β-HSD
PROGESTERONE
17-HYDROXYPROGESTERONE
Δ4-ANDROSTENEDIONE
21-OH
21-OH
17β-HSD
11-Deoxy-Corticosterone (DOC)
11-Deoxycortisol (S)
TESTOSTERONE
11β-OH
11β-OH
Corticosterone
Cortisol (F)
Dihydrotestosterone (DHT)
18-OH
18-OH Corticosterone
18-HSD
Aldosterone

Figure 19.3: Pathogenesis of Congenital Adrenal Hyperplasia (CAH)

- In untreated non–salt-losing females, growth rate and skeletal maturation are accelerated and patients appear muscular.
- Pubic hair appears early (often before the second year of age, acne may be excessive, and the voice may deepen.
- Excessive pigmentation may develop.
- Final adult height is short.

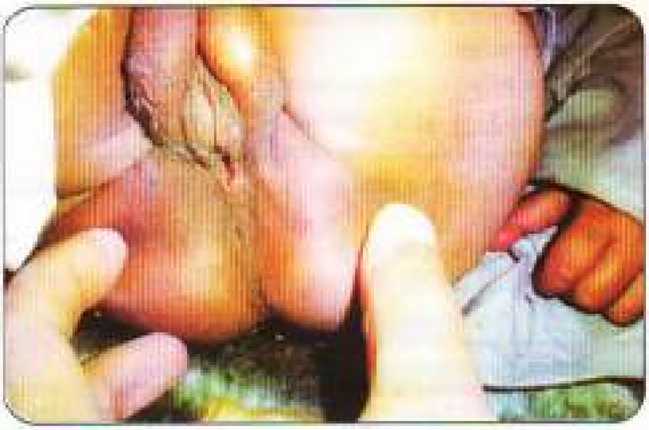


Figure 19.6: A newborn with ambiguous genitalia.

In males: (there is dark pigmentation of scrotum and nipples)

- The male infant usually appears normal at birth but may present with salt-losing crisis usually in the first 2 weeks of life.
- In milder forms, salt-losing crises may not occur. In this condition, enlargement of the penis and increased pigmentation may be noted during the first few months.
- Other clinical findings are similar to those of affected females.
- In the rare isolated defect of 17, 20-desmolase activity, ambiguous genitalia may be present because of impaired androgen production.

Diagnosis

- Karyotype to determine sex
- Buccal smear for bar bodies
- Serum electrolytes (hyponatremia and hyperkalemia).
- Abdominal ultrasonography for pelvic organs (ovaries, uterus). Adrenal ultrasonography, CT scanning, and MRI may be useful in defining pelvic anatomy or enlarged adrenals or in localizing an adrenal tumor. Contrast-enhanced radiographs of the vagina and pelvic ultrasonography may be helpful in describing the internal anatomy in a newborn with ambiguous genitalia.
- Hormonal studies: 17-hydroxyprogesterone concentrations are raised in patients with CAH. Plasma androstenedione concentrations are raised in those patients with excessive androgen synthesis.
- Elevated progesterone levels
- Plasma rennin is elevated in clinical salt wasting and aldosterone level low
- Elevated ACTH levels (not diagnostic)
- Low or undetectable serum cortisol
- Increased urinary 17-ketosteroids

Prenatal diagnosis

- It is necessary if there is an affected child by DNA analysis by chorionic rillous sampling or amniocentesis to detect CYP21 gene.

Prenatal treatment

- A mother at risk is treated with dexamethasone until amniocentesis can provide information about the genetic sex and HLA-type of the fetus.

Management

- Objective of treatment is to achieve normal growth, pubertal development, sexual function, and fertility.
- Glucocorticoid and mineralocorticoid replacement is the main treatment.
- This treatment replaces the deficient hormone and by negative feedback, also suppresses ACTH secretion and androgen production. The efficacy of treatment is monitored by measuring 17-hydroxyprogesterone and androstenedione concentrations in plasma or saliva. Adequacy of mineralocorticoid replacement may be assessed by measuring the plasma rennin activity.
- If the infant presents with a salt losing crisis, high doses of hydrocortisone (30–50 mg/m^2/day in 3–4 divided doses) are required in addition to IV fluids to correct the sodium and water depletion. Glucocorticoid dose can be tapered when electrolyte and fluid depletion is corrected and adrenal crisis is resolved.
- Maintenance therapy for most children with classic 21-OH deficiency is hydrocortisone (15–20 mg/m^2/day) administered orally in 3 divided doses. Dose must be individualized by the patient's clinical course and hormonal levels. Smallest dose of glucocorticoid that can suppress adrenal function are used. About 50% and 60% of the daily dose should be given in the late evening to suppress early morning ACTH rise. Over-treatment with glucocorticoids results in obesity and growth retardation (Cushing syndrome). Under-treatment results in progressive virilization and bone age advancement. Increased doses of glucocorticoids are indicated during periods of stress (e.g. infection or surgery) for both salt-wasting and non-salt wasting patients. Administration of glucocorticoids must be for whole life in all patients with classic forms of CAH.
- Patients who have disturbances of electrolyte regulation (salt-wasting) and elevated plasma rennin activity require a mineralocorticoid and sodium supplementation in addition to glucocorticoids. Maintenance therapy is with fludrocortisone (0.05–0.15 mg given orally once a day) and sodium chloride (1–3 g). Mineralocorticoid replacement sustains

normal electrolyte homeostasis, but excessive mineralocorticoids cause hypertension.

- Vaginoplasty and clitoral recession in female pseudohermaphroditism
- Psychosocial support to the patient and family
- Genetic counseling

Prognosis

- Success in achieving normal height, puberty, sexual function, and fertility is reported with adequate treatment, but there may be short stature, disordered puberty, menstrual irregularity, infertility, inadequate vaginal reconstruction, and lack of sexual function.
- Fertility is normal in males with salt losing form but females with this form may have decreased fertility.
- In simple virilizing form, fertility is unaffected in adequately treated males and females.
- Therapy should be continued throughout life in both males and females to prevent the malignant degeneration of the hyperplastic adrenal gland.

CUSHING SYNDROME

CASE

An 11-year-old boy presents with ***obesity***, ***central fat distribution***, ***arrested growth***, ***hypertension***, ***plethora***, ***purple striae*** and ***osteoporosis***.

- Cushing syndrome may result from excessive secretion of adrenal steroids:
  - Autonomously (adenoma or carcinoma)
  - Excess pituitary ACTH secretion (Cushing disease)
  - Ectopic ACTH secretion
  - Chronic exposure to exogenous glucocorticoid medications

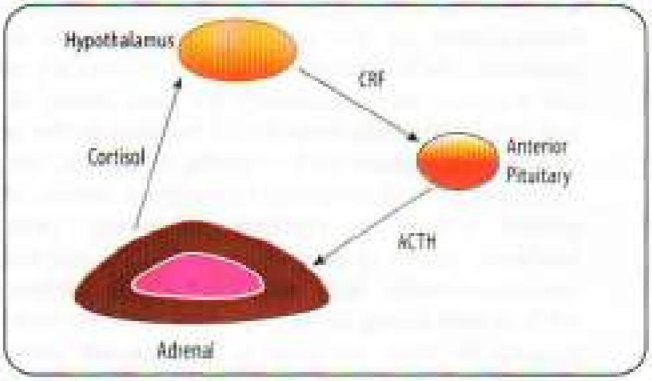


Figure 19.7: Cortisol regulation

Causes of Cushing syndrome

1. ACTH Independent

(Children of less than 7 years of age who have hypercortisolism are most likely to have a primary adrenal cause)

- Iatrogenic

  This is the most common cause of Cushing syndrome. It is due to administration of pharmacologic doses of a glucocorticoid as an anti-inflammatory or immune-suppressive agent.
- Adreno-cortical tumors (e.g. adenoma, carcinoma, micronodular disease).

2. ACTH Dependent (Cushing disease)

(Children of age more than 7 years who have hypercortisolism are more likely to have ACTH-dependent hypercortisolism)

- Hypothalamic CRF-producing tumor
- Pituitary (ACTH-producing) adenoma
- Ectopic CRF-producing tumor (e.g. pancreas, lung)
- Ectopic ACTH-producing tumor (e.g. lung, bronchus, gut).
- Iatrogenic (e.g. ACTH therapy)
- Increased serotonin levels (e.g. idiopathic)

Clinical findings

Excess glucocorticoid

- Obesity with violaceousstriae (obesity is generalized in infants. In older children, it is truncal with moon facies or buffalo hump).
- Decreased height velocity (child has short stature and delayed bone age)
- Plethora (hemoglobin and hematocrit are raised)
- Easy bruisability, ecchymoses
- Osteoporosis
- Glucose intolerance and latent diabetes mellitus
- Poor wound healing
- Increased susceptibility to infections
- Renal stones, hypercalciuria
- Weakness, muscle wasting
- Depression

Excess mineralocorticoid

- Hypokalemia, mild hypernatremia
- Water retention, increased blood volume, edema, and hypertension

Excess androgen

- Hirsutism
- Acne
- Varying degree of virilization
- Menstrual irregularities

Diagnosis

- Cushing syndrome is diagnosed by:
  - Demonstration of high cortisol level
  - Determination of cause of high cortisol level especially in a patient not receiving glucocorticoid treatment
- Plasma cortisol level:
  - Plasma cortisol level elevated, with loss of normal diurnal variation. Determination of cortisol level

between midnight and 2 am may be a sensitive indicator of the loss of diurnal variation.

- Serum ACTH levels:
    - Slightly increased with adrenal hyperplasia (Cushing disease)
    - Decreased in cases of adrenal tumor
    - Greatly increased with ACTH-producing pituitary or extra-pituitary tumors
- Dexamethasone suppression testing:
    - The suppression of adrenal function by a small dose (0.5 mg) of dexamethasone is reduced in adrenal hyperfunction:
    - Larger doses (4–16 mg/d in four divided doses) of dexamethasone cause suppression of adrenal activity when the disease is due to ACTH hypersecretion, whereas hypercortisolism due to adenomas and adrenal carcinomas is not suppressed.
- Serum chloride and potassium levels are lowered.
- Leukocyte count shows polymorpho-nuclear leukocytosis with lymphopenia. Eosinophil count is low.
- Salivary cortisol obtained at midnight is a highly specific and sensitive test for hypercortisolism.
- CRH stimulation test: It is effective test in distinguishing pituitary and ectopic sources of ACTH excess.
- 24 hours urinary free cortisol excretion: This value is raised.
- Radiologic imaging (MRI) studies are performed to visualize a pituitary, adrenal, or ectopic ACTH-producing tumor. Radionuclide studies of the adrenals are indicated in complex cases.

Management

- Removal of the cause of hypercortisolism is the main treatment.
- In all cases of primary adrenal hyperfunction due to tumor, surgical removal is indicated if possible.
- Pituitary microadenomas may respond to pituitary surgery or irradiation.
- In pituitary Cushing disease, medications (cyproheptadine and bromocriptine) are effective in lowering ACTH levels.
- In adrenal adenoma, adrenalectomy is the treatment of choice. In adrenal hyperplasia, a partial adrenalectomy may be performed.

Prognosis

- Prognosis depends on the underlying cause.
- Patients with adrenal or pituitary adenomas have a good prognosis after surgical resection.
- Patients with adrenal or ectopic ACTH-producing carcinomas have a poor prognosis.

DIABETES MELLITUS

CASE

A 14-year-old girl presents with ***frequent urination, excessive thirst*** and hunger. She has the ***rapid loss of weight*** within few months. ***Serum glucose level 250 mg/dL. Urinalysis*** is positive for ***2+ glucose*** but is otherwise normal.

Definition

- Diabetes mellitus is a chronic metabolic disorder resulting from absolute lack of insulin and results in abnormal metabolism of carbohydrate, protein, and fat.
- It is characterized by:
    - Polyuria, polydipsia, and weight loss
    - Hyperglycemia and glucosuria with or without ketonuria
- Diagnosis of DM is made based on four glucose abnormalities:
    - Fasting serum glucose concentration ≥126 mg/dl
    - A random venous plasma glucose ≥200 mg/dl with symptoms of hyperglycemia
    - An abnormal oral glucose tolerance test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dl
    - A HbA1c ≥6.5%

Incidence

- Type I Diabetes Mellitus (DMI) is the most common endocrine disorder in children.
- Peak age of presentation is 5–7 years and at the time of puberty.
- DMI affects approximately 0.7 in 100,000 per year in Karachi.
- Siblings or offspring of a diabetic patient have a 5% risk to develop diabetes.
- Identical twin has a 50% risk.
- Individuals with HLA-DR_3 or HLA-DR_4 or HLA DQ2/8 genotype have 3–4 times increased risk to develop diabetes.
- Individuals with both HLA-DR_3 and–DR_4 alleles have a 10 times increase in risk. There is insulin gene locus IDDM2.

Etiology

- Diabetes mellitus is due to lack of insulin.
- Type I diabetes is characterized by pancreatic islet β-cell destruction mediated by immune mechanisms.
- There is a **genetic predisposition**. HLA antigens DR_3 and DR_4 being generally associated. More than 90% of children with IDDM possess HLA-DR_3, DR_4 alleles, or both.
- **Environmental factors** also play a role in addition to diabetes susceptibility genes to trigger autoimmune

destruction of the islet cells. There is an increased incidence of IDDM in children exposed to cow's milk or cereals (gluten) induce autoimmunity before 2 years of age. There is lower incidence of diabetes among breast fed infants.

- **Viral infections** may be also responsible including coxsackie B virus, cytomegalovirus, mumps, and rubella virus.
- Patients with IDDM have positive glutamic acid decarboxylase antibody (GAD in 80% of patients), insulin autoantibodies (in 100% of cases), and islet cell antibody (ICA in 80–90% of cases).
- **Idiopathic:** Almost 95% of juvenile cases belong to this category. It is believed to be hereditary inborn error of metabolism but exact mode of inheritance is not known. Polygenic (multifactorial) inheritance is suggested.
- **Secondary causes:** Cushing syndrome, hemosiderosis, hyperpituitarism and surgical removal of pancreas.
- Juvenile diabetes is not related to diet or nutritional status of child.

Pathophysiology

- Type 1 diabetes results from immunologic damage to the insulin-producing Beta cells of the pancreatic islets.
- This damage occurs gradually and symptoms do not appear until about 90% of the pancreatic islets have been destroyed.
- Deficiency of insulin results in non-utilization of glucose by the peripheral tissues and hence hyperglycemia.
- The excess glucose causes osmotic diuresis (polyuria) and body tries to compensate that by increasing thirst and large intake of fluids (polydipsia).
- Lack of glucose utilization by the body leads to increased appetite (polyphagia).
- Now body utilizes alternate sources of energy and mobilizes fat from adipose tissue and when rate of free fatty acid exceeds rate of utilization, excess fatty acids are converted to ketone bodies (acetoacetate and beta-hydroxybutyrate) and ketonemia and ketonuria occur.
- Protein synthesis is impaired resulting in loss of weight, muscle wasting, and growth retardation.

Clinical findings

- Diabetes is more acute in onset in children than adults.
- Onset is usually preceded by infection and clinical symptoms include polyuria, polydipsia, polyphagia, and rapid loss of weight.
- Nocturia may be an early symptom in a child who was earlier dry at night.
- Often, diabetic coma is the first manifestation and patient with ketoacidosis presents with:
    - Profound dehydration
    - Hypotension
    - Sunken eyes
    - Dry tongue
    - Kussmaul respiration (rapid and sighing)
    - Lethargy
    - Somnolence
    - Coma
- Recurrent infections and candidiasis may occur.
- On laboratory report, the initial manifestation is postprandial hyperglycemia. Then fasting hyperglycemia develops.

Diagnosis

- Classic symptoms of polyuria, polydipsia, and weight loss are suggestive.
- Diabetes mellitus is also suspected if there are symptoms of diabetes plus random plasma glucose ≥200 mg/dl.
- **Urine examination:**
    - Glycosuria
    - Ketonuria
- **Blood sugar:**
    - Random above 200 mg/dl
    - Fasting above 126 mg/dl
- **Serum electrolytes:**
    - Hyponatremia
    - Hypokalemia
    - Low chloride
- **Acid-base balance:**
    - Bicarbonate base deficit
    - pH is low
- **Blood examination:**
    - Hemoglobin and hematocrit elevated due to dehydration
    - Leukocytosis
- **Glucose tolerance test:** An abnormal Oral Glucose Tolerance Test (OGTT) with a 2-hour postprandial serum glucose concentration ≥200 mg/dl.

Management

- Primary prevention:
    - Prolong breastfeeding
    - Delay cow's milk introduction
    - Delay cereal introduction
- The goals of chronic management include:
    - Adequate nutrition for normal growth and development and an active life
    - Exogenous insulin sufficient to avoid acute clinical manifestations
    - Metabolic control sufficient to minimize long-term complications

Insulin replacement

- The usual insulin-dependent child requires 0.75–1.0 U/kg of insulin daily subcutaneously when the diabetes is fully developed.

- However, during first few months of the disease, the requirement may be less than 0.5 U/kg/day, especially during the 'honeymoon' or remission phase of IDDM.
- The total daily dose is divided between short-acting regular insulin ($1/3^{rd}$ of total dose) and intermediate acting (NPH) insulin ($2/3^{rd}$ of total daily dose).
- It is conventional to give two-thirds of the daily dose before breakfast and one-third before the evening meal.
- Lispro and aspart insulin analog can give better control.
- Insulin pump can be used to give s/c (subcutaneous) insulin and simultaneously monitoring blood sugar levels. Inhaled insulin is also being developed.
- Further adjustment of the dosage is done on results of blood or urine sugar.
- The goal of treatment is to maintain fasting blood sugar between 80–120 mg/dl and post-prandial blood glucose less than 200 mg/dl.
- Oral hypoglycemic agents can be used in type 2 DM.

Diet

- Diet is a cornerstone of diabetes management.
- Children with IDDM require a nutritionally balanced diet with adequate calories and nutrients for normal growth.
- The recommended diet should contain 55% carbohydrate calories, 15% protein, and 30% fat. Mostly carbohydrate calories are complex carbohydrates, and the fat portion should contain low levels of cholesterol and saturated fats.
- Timing of meals and snacks should be to minimize blood glucose variability. Bedtime snacks are important for most children receiving evening NPH doses.
- Diet should be adjusted from the household diet. Avoid refined sugars and give more food with higher fiber content.

Exercise

- Children with IDDM should be encouraged to exercise regularly.
- Regular aerobic exercise at least 25 minutes a day is needed.
- With exercise, insulin requirements are lowered, and metabolic control is improved.
- During exercise, extra calories or lower insulin doses may be needed to prevent hypoglycemia.

Patient/parents education

- Children with IDDM and their families should be taught the principles of home management.
- This training should include:
    - The pathophysiology of diabetes in lay language
    - Insulin types, action, and storage
    - The techniques and timing of insulin injection
    - Home blood glucose monitoring
    - Dietary information
    - The recognition and treatment of hypoglycemia and hyperglycemia
    - Urinary ketone checks
    - Management of diabetes during intercurrent illness
- Education must be appropriate to the child's age and the family's educational background, and it must be ongoing, as the child grows older.

Monitoring

- Blood glucose is monitored:
    - Before meals
    - Before snacks (midmorning, midafternoon, bedtime)
    - In the middle of the night at approximately 3:00 a.m. (the anticipated lowest night-time point), if evening NPH is used
- Two to four recorded readings a day usually provide enough information to assess and achieve control.
- During a period of metabolic instability (during infection or fever, etc), more frequent monitoring is necessary.
- Fasting and pre-prandial blood glucose readings in the 70–150 mg/dl range, post-prandial levels below 180–200 mg/dl, and 3:00 a.m. values above 65 mg/dl indicate good control.
- Doses of regular insulin can be changed using a sliding scale when a specific blood glucose level is outside the target range.

Table 19.1: Sliding Scale of insulin.

Blood glucose level	*Required insulin*
<60 mg/dl	No insulin needed
60–90 mg/dl	0.1 U/kg/dose
90–180 mg/dl	0.2 U/kg/dose
180–270 mg/dl	0.3 U/kg/dose
270–360 mg/dl	0.4 U/kg/dose
>360 mg/dl	0.5 U/kg/dose

- The **measurement of $HbA1_c$ levels** is also helpful in diabetes monitoring. It represents the fraction of hemoglobin to which glucose has been non-enzymatically attached in the bloodstream. Its measurement reflects the average blood glucose concentration of the preceding 2–3 months.
    - The upper limit of normal is 6.5%.
    - **Intensive control** of diabetes mellitus is indicated by $HbA1_c$ level below 6.5%.
- Urine sugar can be checked by **Benedict's test**. 5 ml of Benedict's reagent is taken in a test tube and 8 drops of urine are added. Boil it for 2 minutes and observe

for the color change. Results on the basis of color changes are given below:

Table 19.2: Benedict's test.

Light green:	<0.5 gm% glucose concentration
Green precipitate:	0.5–1.0 gm % glucose concentration
Yellow precipitate:	1–2 gm % glucose concentration
Red precipitate:	>2 gm % glucose concentration

- Urinary ketones should also be monitored, particularly when:
  - The blood glucose levels are above 250 mg/dl.
  - There is fever.
  - There is nausea or vomiting.
  - Child is not feeling well.
- This will detect and prevent diabetic ketoacidosis.

Follow-up

- The main steps to be checked in the follow up clinic are:
  - Growth
  - Blood pressure
  - School progress
  - Dietary compliance
  - HbA_{1C} level
  - Joint mobility
  - Fundus examination
  - Thyroid function tests
  - Injection sites

Complications

- **Brittle diabetes:**
  - Marked fluctuation in control of blood glucose, hypoglycemia or hyperglycemia and ketoacidosis despite frequent adjustment of the dose of insulin.
- **Hypoglycemia:**
  - It is a major and common complication of insulin therapy.
  - Hypoglycemia (insulin reaction) is defined as a blood glucose level below 60 mg/dl.
  - It is characterized by behavior changes, weakness, pallor, diplopia, sweating, nausea, vomiting, tachycardia, palpitations, hunger, abdominal discomfort, disorientation, confusion, dizziness, anxiety or tremors and may progress to convulsions and coma.
  - In severe hypoglycemia, give injection glucagon IM (0.3 mg), or 10% glucose IV (1 ml/kg).
- **Hyperosmolar diabetic coma:**
  - This is characterized by severe hyperglycemia (blood glucose greater than 600 mg/dl), absence of or only slight ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma.
  - There may be neurologic signs (seizures, hemiparesis, etc).
- Diabetic ketoacidosis
- **Peripheral neuritis:** Neuropathy
- **Nephropathy:** Progressive renal failure
- **Retinopathy and blindness**
- **Vasculopathy**
- Hypertension
- Atherosclerosis
- **Infections:** Boils, abscesses, moniliasis, and urinary infection
- **Lipoatrophy**
- **Growth retardation and emotional problems**
- **Somogyi phenomenon:**
  - There is early morning hyperglycemia from midnight hypoglycemia due to excess insulin, and counter-regulatory hormones effect.
- **Dawn phenomenon:**
  - There is early morning hyperglycemia without hypoglycemia due to growth hormone secretion and increased insulin clearance.

Prognosis

- Long-term complications are retinopathy, nephropathy, neuropathy, and macrovascular disease.
- These problems usually occur after 10–15 years of initiation of disease process.
- Some degree of retinopathy is present in nearly 100% of patients with IDDM.
- Macrovascular disease leads to an increased risk of myocardial infarction and stroke.
- Administration of small doses of insulin to at risk individuals for IDDM may delay or prevent the onset of diabetes.

ACUTE DIABETIC KETOACIDOSIS (DKA)

CASE

A 5-year-old boy presents with ***weight loss*** over the previous 2 weeks and night time ***enuresis***. He is increasingly ***confused*** for the last several hours. His breath smelled fruity. On examination, blood pressure is 90/60 mmHg and heart rate 130 beats per minute. ***Mucous membranes*** are ***dry*** and ***respiration*** is ***rapid*** and ***deep*** (Kussmaul breathing). ***Blood glucose*** is ***550 mg/dL***.

Definition

- DKA can be defined as a:
  - Blood glucose level usually greater than 250 mg/dl
  - pH less than 7.25
  - Plasma bicarbonate level of 15mEq/l or less

- Severe DKA is defined as a pH of 7.1 or less and a bicarbonate level of 10 mEq/l or less.
- DKA is a common and potentially life-threatening, acute complication of IDDM. Mortality rates may be as high as 6–10%.

Precipitating factors

DKA may be precipitated in a known diabetic patient by:

- An acute infection
- Omission of insulin dose

Management

The basic steps in the treatment of DKA are:

1. Fluid and electrolyte replacement (especially potassium)
2. Insulin administration

Fluid replacement

- Dehydration is present in nearly all patients with DKA.
- Water and electrolyte losses are mainly due to polyuria (osmotic diuresis by glucosuria), hyperventilation, vomiting, and diarrhea.
- Most patients with DKA are 5% to 10% dehydrated.
- As soon as the diagnosis of DKA is established, adequate IV fluid replacement is given.
- Normal saline or Ringer's lactate are given initially because they are isotonic solutions and restore the intravascular volume and maintain blood pressure and kidney perfusion. This enhances the glucose loss through the kidney and results in a lower blood glucose level.
- Fluid deficit = 100 ml × W_t (kg)
- Fluid required = Fluid deficit + Maintenance fluid
- Always assume that child is 10% dehydrated (needs 100 ml/kg fluid).
- Give maintenance fluid as given in the table.

Table 19.3: Body weight with its fluid maintenance requirements

Body weight (kg)	*Fluid maintenance requirements*
Up to 10	100 ml/kg
10–20	1000 ml + 50 ml/kg over 10 kg
>20	1500 ml + 20 ml/kg over 20 kg

For example, a 10 kg child with DKA presents with 10% dehydration.

Fluid deficit = 100 × 10 = 1000 ml

Maintenance fluid = 100 × 10 = 1000 ml

Fluid needed for replacement = 1000 + 1000 = 2000 ml

Insulin therapy

- Insulin should be given as a continuous IV infusion.
- The usual recommended dose is 0.1 U/kg/hour.
- Fluids used for making insulin infusion should be deducted from total fluids for replacement.
- The insulin infusion is given separately from the replacement fluids so the rates can be adjusted independently.

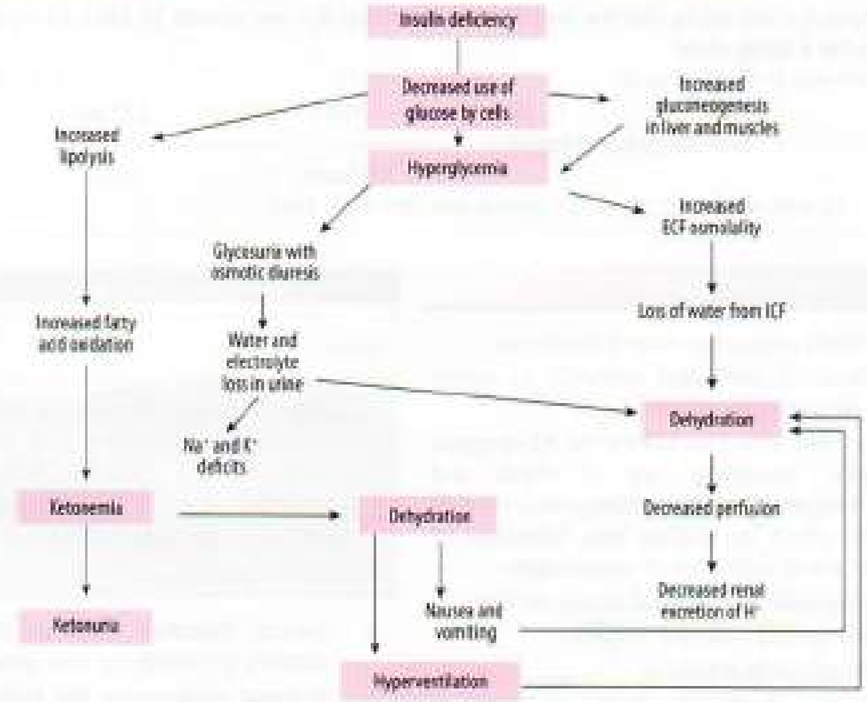

Insulin deficiency
Decreased use of glucose by cells
Increased gluconeogenesis in liver and muscles
Increased lipolysis
Hyperglycemia
Increased ECF osmolality
Glycosuria with osmotic diuresis
Loss of water from ICF
Increased fatty acid oxidation
Water and electrolyte loss in urine
Dehydration
Na⁺ and K⁺ deficits
Ketonemia
Dehydration
Decreased perfusion
Decreased renal excretion of H⁺
Ketonuria
Nausea and vomiting
Hyperventilation

Figure 19.8: Pathogenesis of DKA.

- If the blood glucose level decreases to 250 mg/dl and acidosis persists, glucose is given as 5% dextrose and may be increased to 10% dextrose to keep the blood glucose approx 250 mg/dl.
- Measure glucose every hour; electrolytes and acid-base every 2–4 hours for the first 24 hours.

Bicarbonate

- Bicarbonate is given when there is severe acidosis (pH <7.0–7.1) causing respiratory or cardiac disturbances.
- Bicarbonate is given to raise pH to 7.2 in a dose of 1–2 mEq/kg over 2 hours.

Treatment of infection

- Appropriate antibiotics are given to control any infection.

Converting to subcutaneous insulin

- Change to subcutaneous injection should only be carried out when:
    - Patient is conscious and taking orally.
    - There is no evidence of metabolic acidosis.
    - Blood sugar level is 180–240 mg/dl.
    - Any identified precipitating factor (e.g. infection) should have been treated.
- Dose of subcutaneous insulin may be adjusted by sliding scale method.

Table 19.4: Diabetic ketoacidosis treatment protocol.

Time	Therapy	Comments
1st hr	10.20 ml/kg IV bolus 0.9% NaCl or LR insulin drip at 0.05 to 0.10 units/kg/hr	Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral
2nd hours until DKA	0.45% NaCl: plus continue insulin drip 20 mEq/L KPhos and 20 mEq/L KAc 5% glucose if blood sugar >250 mg/dL (14 mmol/L)	$\text{IV rate} = \dfrac{\text{85 ml/kg+maintenance-bolus infusion}}{\text{23 hour}}$ If K <3 mEq/L, give 0.5–1.0 mEq/kg as oral K solution or increase IV K to 80 mEq/L
Variable	Oral intake with subcutaneous insulin	No emesis; CO_2 ≥16 mEq/L; normal electrolytes

Note that the initial IV bolus is considered part of the total fluid allowed in the first 24 hours and is subtracted before calculating the IV rate.

Maintenance (24 hours) = 100 ml/kg (for the first 10 kg) + 50 ml/kg (for the second 10 kg) + 25 ml/kg (for all remaining kg)

Sample calculation for a 30 kg child:

1st hour = 300 ml IV bolus 0.9% NaCl or LR

$$\text{2nd and subsequent hours} = \frac{(85\text{ ml} \times 30) + 1750\text{ ml} - 300\text{ ml}}{23\text{ hours}} = \frac{175\text{ ml}}{\text{hour}}$$

(0.45% NaCl with 20 mEq/L Kphos and 20 mEq/L Kac)

DIABETES INSIPIDUS

- It manifests clinically with polyuria and polydipsia.
- Vasopressin release is controlled primarily by serum osmolality and intravascular volume.
- Vasopressin exerts its effect on kidney via V2 receptor on renal tubule, ascending loop of Henle and periglomerular tubules. The 'Atrial Natriuretic Peptide (ANP)' exerts its effect by sodium loss, inhibition of sodium resorption and inhibition of vasopressin.
- Disorders of vasopressin release and action include:
    - Central (neurogenic) diabetes insipidus
    - Nephrogenic diabetes insipidus
    - The syndrome of inappropriate secretion of antidiuretic hormone

Central diabetes insipidus

CASE

Central diabetes insipidus: A 10-year-old boy presents with ***excessive urination*** and thirst. ***No other family member*** has this complaint. A urine analysis shows no glucose and ketones. ***Urine specific gravity*** is ***1.005***. He improves (***urine concentrates***) when parenteral ***DDAVP*** is administered.

- Central Diabetes Insipidus (DI) is characterized by inability to synthesize and release vasopressin.
- Without vasopressin the kidneys cannot concentrate urine, causing excessive urinary water loss.

Nephrogenic diabetes insipidus

CASE

Nephrogenic diabetes insipidus: A 4-year-old child presents with ***failure to thrive***, ***frequent urination***, ***excessive thirst***. Weight has decreased 4 kg in the past 4 months. ***Other family members have similar histories*** for many years. A urine analysis shows ***no glucose***, ketones, or evidence of a urinary tract infection. ***Specific gravity*** is less than 1.005. ***Urine not concentrates*** when parenteral ***DDAVP is administered***.

- Nephrogenic diabetes insipidus is a hereditary congenital disorder in which the urine is hypotonic and produced in large volumes because the kidneys fail to respond to antidiuretic hormone.

Etiology

Central diabetes insipidus

- Genetic (autosomal dominant)
- Acquired
- Trauma (surgical or accidental)
- Congenital malformations (holoprosencephaly, septo-optic dysplasia, encephalocele)
- Neoplasms (craniopharyngioma, germinoma, metastasis)
- Infiltrative (Langerhans cell histiocytosis), autoimmune (lymphocytic infundibuloneurohypophysitis), and infectious diseases
- Drugs (chemotherapy)
- Idiopathic

Nephrogenic diabetes insipidus

- Genetic (X-linked, autosomal recessive, autosomal dominant)
- Acquired
- Hypercalcemia, hypokalemia
- Drugs (lithium, demeclocycline)
- Kidney disease
- Primary polydipsia
- Sickle cell anemia

Clinical findings

- Infant can present with irritability, failure to thrive, fever with polyuria and polydipsia.
- Onset of symptoms of excessive thirst and urination is abrupt, with nocturia.
- Caloric intake diminishes.
- Growth and weight gain may decrease.
- If the diabetes insipidus is secondary to a tumor there may be neurologic and visual complaints.

Diagnosis

- DI is confirmed when **serum hyperosmolality** is associated with **urine hypoosmolarity**.

Diagnostic findings

- Polydipsia, polyuria (>2 L/m^2/d), nocturia, dehydration, and hypernatremia
- Inability to concentrate urine after fluid restriction (urine specific gravity <1.010 and urine osmolality <300 mOsm/kg)
- Plasma osmolality >300 mOsm/kg with urine osmolality <300 mOsm/kg
- Low plasma vasopressin with antidiuretic response to exogenous vasopressin
- Also get serum Na$^+$, K$^+$, urea, creatinine, glucose and calcium levels.

Water deprivation test

- If the child's first morning urine is diluted (specific gravity <1.015), a water deprivation test must be done.
- A diagnosis of diabetes insipidus is made in the presence of a plasma osmolality >300 mOsm/kg of water with an inappropriate low urine osmolality.
- The child is then given a dose of DDAVP (desmopressin) and the urine and plasma osmolality measured.
- A rise in urine concentration confirms a diagnosis of central diabetes insipidus.
- A child with nephrogenic diabetes insipidus will fail to concentrate urine after DDAVP.

Differential diagnosis

- Psychogenic polydipsia
- Diabetes mellitus
- Hypertonic dehydration secondary to diarrhea
- Exogenous salt administration

Management

- Central DI is treated with oral (25-300µg every 8–12 hour) or intranasal (10 µg/0.1 ml) desmopressin acetate (DDAVP).
- Children hospitalized with acute DI can be managed with intravenous vasopressin.
- Due to the amount of antidiuresis, intravenous fluids will need to be restricted to avoid water intoxication.
- Infants with DI should not be treated with DDAVP. Treatment with DDAVP in association with formula milk or breast milk may cause water intoxication because the water intake exceeds the capacity for renal clearance. Infants are treated with extra free water, rather than DDAVP, to maintain normal hydration.
- For nephrogenic diabetes insipidus following treatments are given:
    - Provision of ample fluids at all times
    - Elimination of underlying disorder (offending drugs, hypercalcemia, hypokalemia or ureteral obstruction)
    - Thiazide diuretics (promote sodium diuresis and volume concentration)

- Prostaglandin inhibitors such as indomethacin (2 mg/kg per day) enhance proximal tubular sodium and water reabsorption

RICKETS

CASE

A 2-year-old boy presents with complaint of his ***inability to walk***. He has off and on history of diarrhea and vomiting. He is taking only over diluted milk ***without adequate complementary feeding***. He also has mildly delayed motor milestones. On examination, weight is 9 kg and height is 78 cm. He is otherwise well. Anterior ***fontanel*** is ***open***.

Definition

- It is defined as failure of mineralization of growing bone or osteoid tissue. (Failure of mature bone to mineralize is called osteomalacia).

Main points

- Rickets is a metabolic disturbance of bone growth and results from dietary lack of vitamin D or ultraviolet rays of sunlight.
- An infant requires only 30 minutes per week of total body sun exposure or 2 hours per week of head exposure to maintain adequate vitamin D status.
- It is a common disease of tropics and subtropics.
- Rickets is a disease of rapidly growing bones and usually occurs in the first 2 years of life.
- If it persists beyond 2 years of age, then consider vitamin D resistant rickets (renal rickets).
- Deficiency may occur in dark-skinned infants (inadequate penetration of sunlight) or in breast fed infants of mothers unexposed to sunlight.

Vitamin D metabolism

- The major function of Vitamin D is the maintenance of normal plasma levels of calcium and phosphorus.
- It is required for the prevention of bone diseases (rickets, osteomalacia) and of hypocalcemictetany.

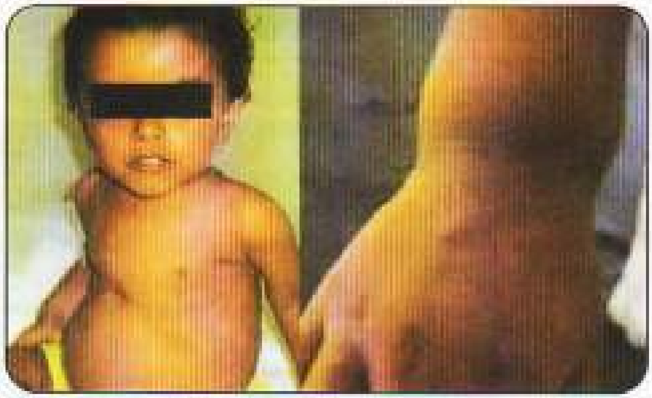


Figure 19.9 : A child with chest deformity and widening of wrists due to rickets.

- Vitamin D participates in the:
  - Absorption of calcium and phosphorus from the intestine
  - Mobilization of calcium from bone
  - Reabsorption of phosphorus from the kidneys
- Two forms of vitamin D are active in man. Vitamin D_2 (ergocalciferol) and Vitamin D_3 (cholecalciferol).
- Human skin contains 7-hydrocholesterol, which is converted by UV rays of sunlight into Vitamin D_3, which is absorbed into the blood.
- Sunlight, which has passed through window glass, lacks UV rays.
- Depending on the skin's level of melanin pigmentation, which absorbs UV light, and the amount of exposure to sunlight, about 80% of the Vitamin D needed can be endogenously derived. The remainder must be obtained from dietary sources.
- Vitamin D_3 is bound to an alpha-1 globulin and transported to the liver.
- In the liver, it is hydroxylated to 25-hydroxy-cholecalceferol [25-OH-D] and is converted in the kidney to 1,25-dihydroxy-cholcalceferol [1,25-$(OH)_2$-D] by alpha-1 hydroxylase.

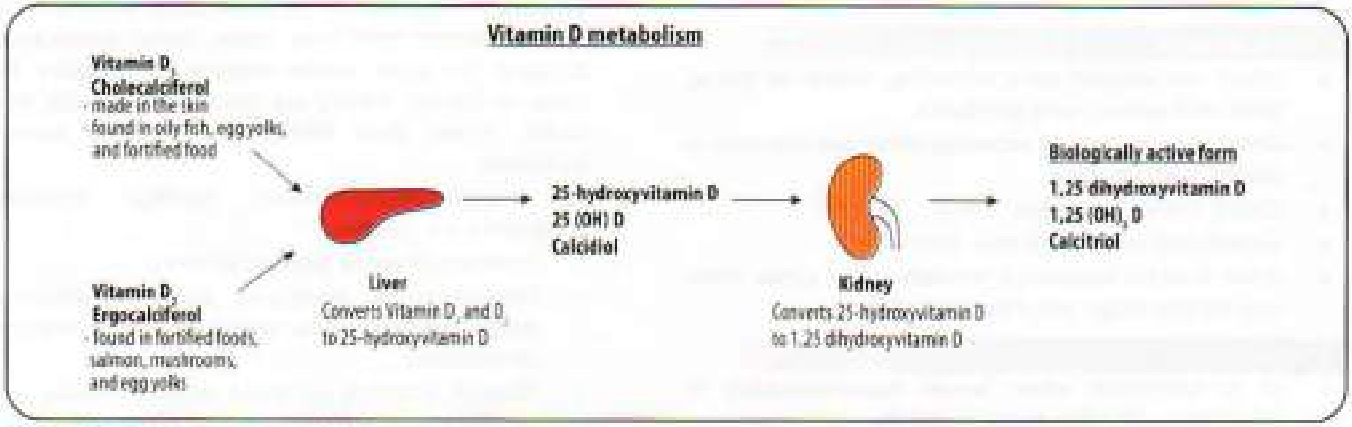

Vitamin D metabolism
Vitamin D3
Cholecalciferol
-made in the skin
-found in oily fish, egg yolks, and fortified food
Vitamin D2
Ergocalciferol
-found in fortified foods, salmon, mushrooms, and egg yolks
Liver
Converts Vitamin D3 and D2 to 25-hydroxyvitamin D
25-hydroxyvitamin D
25 (OH) D
Calcidiol
Kidney
Converts 25-hydroxyvitamin D to 1.25 dihydroxyvitamin D
Biologically active form
1.25 dihydroxyvitamin D
1,25 (OH)2 D
Calcitriol

Figure 19.10: Vitamin D metabolism

- 1,25-(OH)$_2$-D is the most active metabolite of vitamin D and it is best regarded as a steroid hormone. It acts on the GIT to increase calcium absorption and on bone to increase calcium resorption.
- Parathyroid hormone activates the alpha-1 hydroxylase enzyme in kidney.

Pathology

- Defective growth of bone in rickets results from lack of normal growth of epiphyseal cartilage and its calcification due to decrease in the calcium and phosphorus salts.
- The growth at the distal end of epiphyseal plate continues so that epiphyseal end expands and increases in thickening causing widening of wrist and ankles and rachitic rosary of ribs.
- Due to continued growth of epiphysis its end become irregular, frayed and end is cup shaped.
- There is also general softening of the bone, so curvature and deformities of legs appear and there is craniotabes.

Causes of rickets

Vitamin D disorders

- Nutritional vitamin D deficiency
- Congenital vitamin D deficiency
- Secondary vitamin D deficiency
- Malabsorption
- Increased degradation (phenobarbitone, phenytoin)
- Decreased liver 25-hydroxylase
- Vitamin D–dependent rickets type 1
- Vitamin D–dependent rickets type 2
- Chronic kidney disease

Calcium deficiency

- Low calcium intake
- Diet deficient in calcium
- Premature infants (rickets of prematurity)
- Malabsorption
- Dietary inhibitors of calcium absorption

Phosphorus deficiency

- Inadequate intake
- Premature infants (rickets of prematurity)

Renal losses

- X-linked hypophosphatemic rickets
- Autosomal dominant hypophosphatemic rickets
- Autosomal recessive hypophosphatemic rickets
- Hereditary hypophosphatemic rickets with hypercalciuria
- Distal renal tubular acidosis

Types of rickets

Vitamin D deficient rickets (Nutritional rickets)

- Lack of vitamin D in the diet results in decreased calcium absorption in the intestine.
- If mother is malnourished and breastfeeding and baby is fed unfortified milk without vitamin supplement.
- High dietary fiber interferes with calcium absorption.

Vitamin D dependent rickets

- It is an inborn error of Vitamin D metabolism transmitted as autosomal recessive and is divided into type 1 and 2.

Type I

- Type 1 is secondary to a defect in the renal 1-alpha-hydroxylase responsible for the synthesis of 1, 25-dihydroxy Vitamin D$_3$ from 25-hydroxy Vitamin D$_3$.
- Symptoms usually appear within the first year of life.
- There is hypocalcemictetany, convulsions, muscle weakness, and growth failure.
- Hypocalcemia (often <8 mg/dl) is a cardinal feature.
- Diagnosis is made by a normal serum 25-OH-D$_3$ level and a low or undetectable serum 1,25-(OH)2-D$_3$ level.

Type 2

- Type 2 is due to end-organic resistance to the effect of 1,25-(OH)$_2$-D$_3$.
- The defect is in the binding of the metabolite.
- Clinical and radiological findings of rickets are same as type 1.
- Alopecia is seen in severe resistance to 1,25-(OH)$_2$-D$_3$ and is due to dysfunction of target cells in hair follicles.
- Biochemically, level of 1,25-(OH)$_2$-D$_3$ is very high.

Vitamin D resistant rickets (X-linked hypophosphatemia; Familial hypophosphatemia)

CASE

Hypophosphatemic rickets: A 7-year-old boy presents with bowing of legs and waddling gait. On examination, his height is on 5th percentile for his age. Investigations show serum level of calcium is 9 mg/dl, serum phosphate is 1.0 mg/dll and alkaline phosphatase is 1500 IU/L, serum creatinine is 1.0 mg/dl. Mother has height of 143 cm.

- Males are more severely affected than females.
- This is the most common non-nutritional form of rickets.
- Both vitamin D activation and tubular reabsorption of phosphate are impaired, resulting in hypophosphatemia.
- As this is usually an X-linked dominant condition, some mothers of affected children may have features of the disease such as bowing or short stature, whereas some mothers only have fasting hypophosphatemia.
- At the age of walking due to weight bearing, children with familial hypophosphatemia present with bowing of the lower extremities.

Table 19.5: Types and biochemical changes in rickets.

Type	Ca	PO$_4$	ALP	PTH	25(OH)D3	1,25(OH)$_2$D$_3$
Vitamin D deficient	↓ or N	↓ or N	↑	↑	↑	↓ or N
Vitamin D dependent type I	↓	↓ or N	↑↑	↑	N	↓↓
Vitamin D dependent type II	↓	↓ or N	↑↑	↑	N	↑
X-linked hypophosphatemia	N	↓↓	↑	N	N	N or ↓
Hypophosphatemic bone disease	N	↓↓	↑	N	N	N
Hereditary hypophosphatemic rickets with hypercalciuria	N	↓↓	↑	Nor ↓	N	↑

- Rachitic rosary, Harrison sulcus, and profound myopathy are not present.
- Biochemical abnormalities and radiographic signs of rickets may appear in the first few months of life.
- Abnormalities of tooth structure may bring about early and extensive caries.

Rickets due to malabsorption

- Children with malabsorption, such as celiac disease, steatorrhea, or cystic fibrosis may develop rickets due to deficient absorption of Vitamin D and calcium.

Renal rickets

- There may be proteinuria, hematuria, UTI or polyuria with CRF or Fanconi syndrome.
- Renal osteodystrophy (osteopenia, osteitis fibrosis, rickets) is due to decreased activity of 1-alpha hydroxylase in the kidneys.

Hepatic rickets

- This occurs in chronic liver disease, such as biliary atresia and other cholestatic diseases.
- It results from decreased intestinal absorption of Vitamin D (a fat soluble vitamin) or from decreased 25-hydroxylation in the liver itself.

Rickets associated with Renal Tubular Acidosis (RTA)

- In proximal RTA, hypophosphatemia and rickets results from hypochloremic metabolic acidosis and persistent alkaline urine, interfering with phosphate resorption.
- In distal RTA (type 1), bone dissolution occurs because the calcium carbonate of bone serves as a buffer against the persistent metabolic acidosis.

Rickets due to chronic anticonvulsant therapy

- Chronic anticonvulsant therapy with combination of phenytoin and phenobarbitone causes increased metabolism of calcidiol and may be associated with rickets.
- This is due to hepatic dysfunction in the conversion of vitamin D, caused by the anticonvulsant induced cytochrome P-450 hydroxylation enzymes.

Hypophosphatasia

- This is a rare autosomal recessive disorder.
- It is caused by an enzymatic defect in alkaline phosphatase activity.
- A low serum alkaline phosphatase level confirms diagnosis.
- Children who survive this condition may improve spontaneously when they mature.

Clinical findings

- Rickets is a disease of growing bones and peak incidence is between 6 months to 2 years of age.
- Early manifestations are FTT, irritability, profuse sweating while asleep, hypotonia and associated findings of iron-deficiency anemia and respiratory infections.
- The following are the signs of rickets:

Head

- Head may be larger than normal
- Frontal bossing (due to an excess of osteoid).
- Craniotabes (a ping pong ball sensation); this is due to thinning of the outer table of the skull. This can be demonstrated by pressing firmly over the occiput or posterior parietal bones. Craniotabes may disappear before the end of the 1st year.
- Delayed closure of the fontanel. It is larger than normal.
- Caput quadratum (square-like head)

Teeth

- Delayed eruption of temporary teeth
- Defective enamel and caries
- Calcification of permanent teeth may be affected

Thorax

- Rachitic rosary (prominent costo-chondral junctions)
- Harrison's sulcus (depression above the subcostal margin at the site of attachment of diaphragm)
- Pigeon chest deformity (anterior curvature of sternum)

Spine

- Kyphosis, scoliosis, lordosis

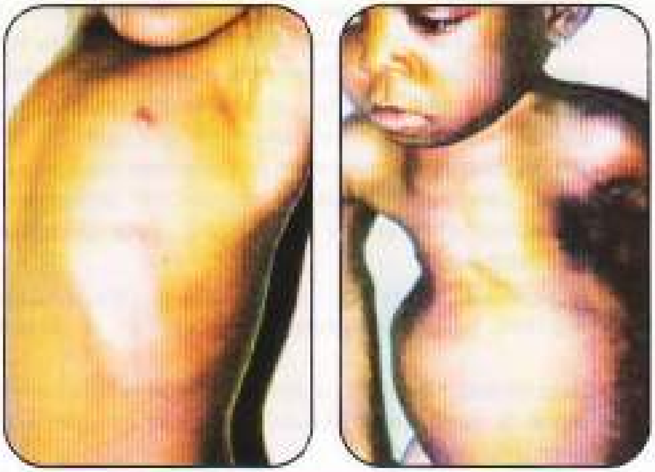


Figure 19.11: Harrison's sulcus in rickets.

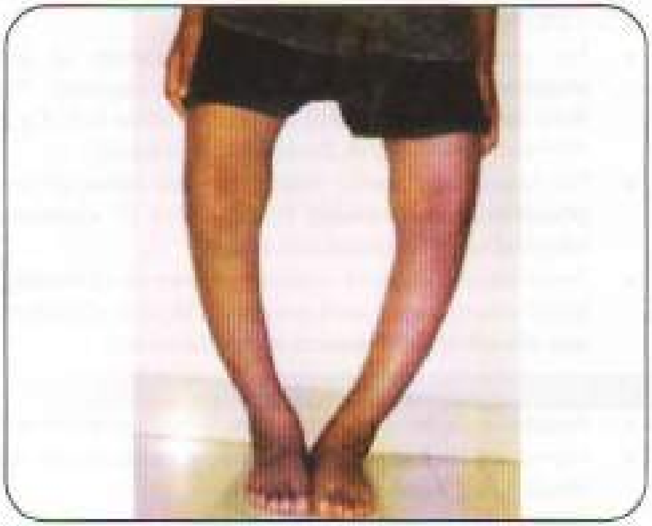
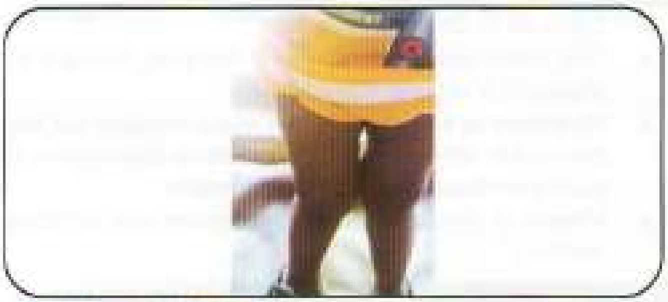
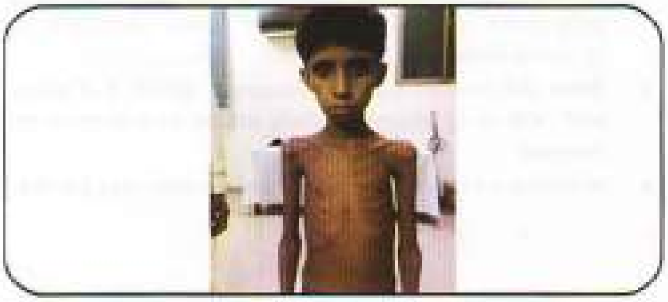


Figure 19.12: Bowing of legs in rickets.



Knock knee in rickets.



Rickety rosary prominent costochondral junction.

Anterior bowing of legs

Pelvis

- Contracted pelvis (which is hazardous to child birth)

Extremities

- Widening of wrists, ankles, and other epiphyses
- Bending of long bone results in bow legs or knock knees (genu valgum)
- Greenstick fractures

Miscellaneous

- Hypotonia and potbelly
- Laxity of ligaments
- Short stature
- Tetany

Diagnosis

- **History** of inadequate vitamin D intake and no exposure to sunlight.
- **Clinical manifestations.**
- **Biochemical changes** (biochemical and radiological abnormalities may precede the clinical signs).
  - Serum calcium is low (normal 9–11 mg/dl).
  - Serum phosphorus is slightly decreased (normal 5–7 mg/dl).
  - Alkaline phosphatase is raised (normal 50–200 IU). This is the most striking biochemical feature, reflecting increased but ineffective activity of osteoblasts.
  - Confirmation of vitamin D deficiency can be made by measurement of plasma metabolite levels and a plasma 25-(OH)-D of less than 20 ng/l supports the diagnosis.
- **X-ray changes:**
  Active rickets (best site for X-ray is wrist joint).
  - There is cupping, fraying and flaring of long bones.
  - Distance between epiphysis and diaphysis is increased.
  - Bone density is decreased but trabeculae are prominent.

Healing rickets

- There is sharp line of preparatory calcification at the distal end of the shaft.
- Gradually, osteoid tissue is calcified.

Differential diagnosis

- Scurvy
- Congenital epiphyseal dysplasia
- Chondrodystrophy

Management

- Children with nutritional vitamin D deficiency should receive vitamin D and adequate nutritional intake of calcium and phosphorus.
- With stoss therapy, 300,000–600,000 IU of vitamin D is administered orally or intramuscularly as 2–4 doses over 1 day. Other strategy is daily, high-dose vitamin D, with doses ranging from 2,000–5,000 IU/day over 4–6 weeks. Either strategy should be followed by daily vitamin D intake of 400 IU/day if <1 year old or 600 IU/day if >1 year old.

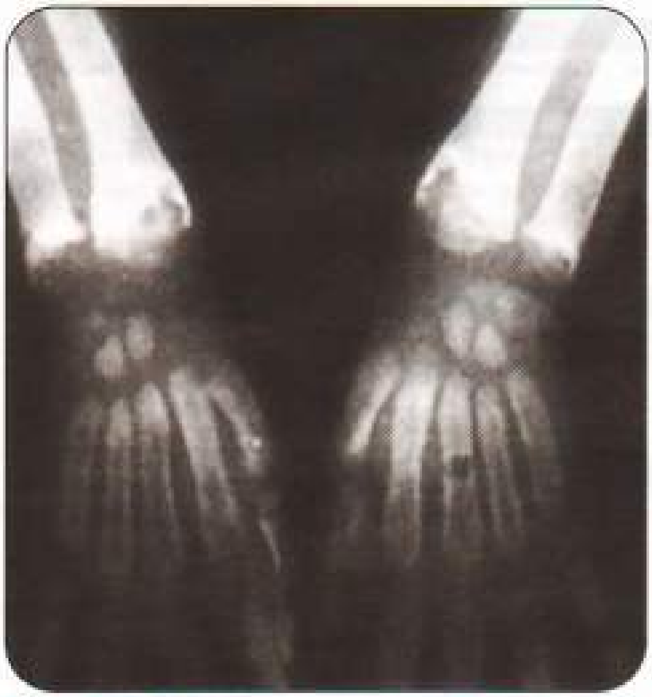


Figure 19.13: Radiographic appearance of wrists in rickets. Note cupping and fraying of long bones.

- Children should receive adequate dietary calcium and phosphorus (from milk and other dairy products).
- Treatment of vitamin D deficiency due to malabsorption requires high doses of vitamin D. Because of its better absorption, 25–D (25–50 μg/day or 5–7 μg /kg/day) is superior to Vitamin D$_3$. The dose is adjusted based on monitoring of serum levels of 25–D.
- Children with vitamin D–dependent rickets type 1, respond to long-term treatment with 1,25-D (calcitriol). Initial doses are 0.25–2 μg/day, and lower doses are used once the rickets has healed. It is important to ensure adequate intake of calcium.
- Patients with vitamin D–dependent rickets type 2 respond to extremely high doses of Vitamin D$_2$, 25-D or 1,25-D, especially patients without alopecia. This response is due to a partially functional vitamin D receptor. All patients with this disorder should be given a 3–6 month treatment of high-dose vitamin D and oral calcium. Treatment of patients who do not respond to vitamin D is difficult.
- For renal rickets, therapy requires the use of a form of vitamin D that can act without 1-hydroxylation by the kidney (calcitriol), which permits adequate absorption of calcium and directly suppresses the parathyroid gland. Because hyperphosphatemia is a stimulus for PTH secretion, normalization of the serum phosphorus level via a combination of dietary phosphorus restriction and the use of oral phosphate binders is also important.
- Rickets secondary to inadequate dietary calcium requires adequate calcium, typically as a dietary supplement. Vitamin D supplementation is necessary if there is concurrent vitamin D deficiency. Doses of elemental calcium are:
- 700 mg/day for 1–3 years of age
- 1,000 mg/day for 4–8 years of age
- 1300 mg/day for 9–18 years of age
- For phosphorus deficiency a combination of oral phosphorus and 1,25-D (calcitriol) is required. The daily need for phosphorus supplementation is 1–3 g of elemental phosphorus divided into 4–5 doses.
- For hypophosphatemic rickets therapy relies on oral phosphorus replacement (1–2.5 g/day of elemental phosphorus in 5 divided oral doses).
- Renal tubular acidosis requires regular alkali therapy, but if rickets is seen with proximal RTA, oral phosphate and vitamin D supplements should be added.

Complications

- Respiratory infections (bronchitis, bronchopneumonia)
- Pulmonary atelectasis due to severe deformity of the chest.
- Anemia due to iron deficiency or infections

Prevention

- Exposure to UV light (sunlight).
- Oral administration of vitamin D (daily requirement of vitamin D is 10μg or 400 IU).
- Premature or breast-fed babies whose mothers are not exposed to adequate sunlight should receive vitamin D supplementation daily to prevent rickets.
- Vitamin D should be given to pregnant and lactating mothers.

Prognosis

- Healing begins within a few days (2–3 weeks) when sufficient amounts of vitamin D are given. Healing progresses slowly and normal body structure is restored (6 months to one year).
- Bone deformities usually disappear within 1–2 years with 400 IU of vitamin D daily intake as maintenance therapy.
- In advanced cases, permanent deformities may persist.

CHAPTER 20

Metabolic Diseases

INBORN ERRORS OF METABOLISM

CASE

A baby girl was ***normal at birth*** but on second day of life she presented with ***vomiting*** and ***collapsed***. Her parents are first ***cousins***. They have previously lost a baby in the first week of life. Blood glucose is low and she has metabolic acidosis.

An approach to inborn errors of metabolism

- Many childhood conditions are caused by gene mutations. These genes encode specific proteins.
- These gene mutations can result in the alteration of primary protein structure or the amount of protein synthesized.
- The functional ability of protein (e.g. an enzyme, receptor, transport vehicle, membrane, or structural element) may be relatively or seriously compromised.
- These hereditary biochemical disorders are collectively termed as inborn errors of metabolism.
- Severe forms of inborn errors of metabolism usually present in the newborn period or shortly thereafter.
- Children with inborn errors of metabolism may present with one or more of a large variety of signs and symptoms. These may include :
    - Metabolic acidosis
    - Persistent vomiting
    - Failure to thrive
    - Developmental delay
    - Hypoglycemia
    - Elevated blood or urinary levels of a particular metabolite (an amino acid, organic acid, ammonia)
    - A peculiar odor
    - Physical changes such as hepatomegaly
- Separating the conditions presenting in the neonatal period from the conditions presenting in children can help the diagnosis.

Inborn errors of metabolism presenting in neonatal period

- Inborn errors of metabolism presenting in neonatal period are usually severe and lethal if not properly treated.
- Clinical findings are usually nonspecific and similar to sepsis.
- An inborn error of metabolism should be suspected in a severely ill neonatal infant, and special studies should be undertaken if highly suspected.
- Infants with metabolic disorders are usually normal at birth.
- Lethargy, poor feeding, convulsions, and vomiting may develop as early as a few hours after birth.
- A history of clinical deterioration in a previously normal neonate should suggest an inborn error of metabolism.
- Occasionally, vomiting may be severe enough to suggest intestinal obstruction.
- Lethargy, poor feeding, convulsions, and coma may also be seen in infants with hypoglycemia or hypocalcemia.
- Most inborn errors of metabolism are inherited as autosomal recessive traits. A history of consanguinity and/or death in the neonatal period is important and increases the suspicion of inborn errors of metabolism.
- Physical examination usually reveals nonspecific findings. Most signs are related to the central nervous system.
- Hepatomegaly is a common finding in many inborn errors of metabolism.
- Occasionally, a peculiar odor may aid to the diagnosis.
    - Glutaric academia type II (sweaty feet, acrid).
    - Hawkinsinuria (swimming pool)
    - Maple syrup urine disease (burnt sugar)
    - Hypermethioninemia (boiled cabbage)
    - Multiple carboxylase deficiency (tomcat urine)
    - Phenylketonuria (mousey or musty)
    - Trimethylaminuria (rotting fish)
    - Tyrosinemia (boiled cabbage, rancid butter)
- Diagnosis usually requires a variety of specific laboratory studies.
- Measurements of serum concentrations of ammonia, bicarbonate, and pH are very helpful in differentiating major causes of metabolic disorders.
- Elevation of blood ammonia is usually caused by defects of urea cycle enzymes.
- Infants with elevated blood ammonia levels from urea cycle defects commonly have normal serum pH and bicarbonate value.
- Elevation of serum ammonia is also observed in organic acidemias.
    - These infants are severely acidotic (↓pH) because of accumulation of organic acids in body fluids.

- When blood ammonia, pH, and bicarbonate values are normal, other aminoacidopathies (such as hyperglycinemia) or galactosemia should be considered.
- Galactosemic infants may have other features (cataracts, hepatomegaly, ascites, and jaundice).
- Specific diagnosis even in dying infant is important for genetic counseling of the family.
- A specific diagnosis may be established by:
  - Measurement of abnormal metabolites in body fluids
  - Assay of the specific enzyme activity
  - Identification of the mutant gene

Children after the neonatal period

- Most inborn errors of metabolism that cause few symptoms in neonatal period may remain undiagnosed for months or even years.
- Early clinical manifestations in children with these forms are commonly nonspecific and may be attributed to perinatal insults.
- In older children, common clinical manifestations are mental retardation, motor deficits, developmental regression, convulsions, myopathy, recurrent emesis, and cardiomyopathy.
- Episodes of acute clinical manifestations may be separated by periods of disease-free states.
- The episodes are usually triggered by stress or an infection.
- The child may die during one of these acute attacks.
- An inborn error of metabolism should be considered in any child with one or more of the following manifestations:
  - Unexplained mental retardation
  - Developmental delay or regression
  - Motor deficit
  - Convulsions
  - Unusual odor, particularly during an acute illness
  - Intermittent episodes of unexplained vomiting, acidosis, mental deterioration, or coma
  - Hepatomegaly
  - Renal stones
  - Muscle weakness or cardiomyopathy

Classification of metabolic diseases

- Metabolic diseases can be categorized according to the different nutritional components in which the aberrant metabolism may be found:

Protein metabolism disorder

- Amino acid metabolism (screened with urine organic acids and serum amino acids levels):
  - Phenylketonuria
  - Maple syrup urine disease
  - Tyrosinemia, type I
  - Homocystinuria
- Urea cycle disorders (screened with serum ammonia level).

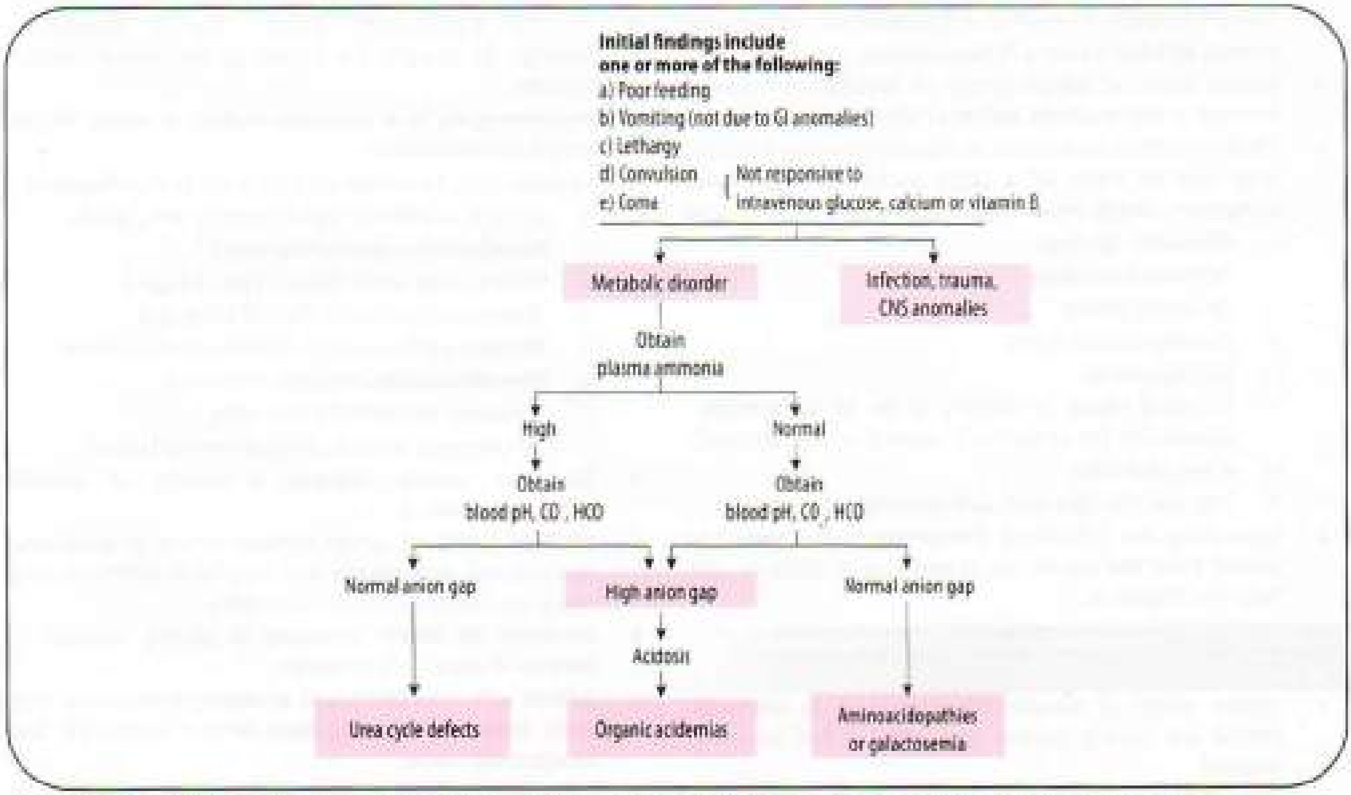

Initial findings include
one or more of the following:
a) Poor feeding
b) Vomiting (not due to GI anomalies)
c) Lethargy
d) Convulsion
e) Coma
Not responsive to
intravenous glucose, calcium or vitamin B
Metabolic disorder
Infection, trauma, CNS anomalies
Obtain plasma ammonia
High
Normal
Obtain blood pH, CO , HCO
Obtain blood pH, CO , HCO
Normal anion gap
High anion gap
Normal anion gap
Acidosis
Urea cycle defects
Organic acidemias
Aminoacidopathies or galactosemia

Figure 20.1: Initial clinical approach to a full term newborn infant with a suspected genetic metabolic disorder

Carbohydrate metabolism disorders

- Glycogen storage diseases
- Galactosemia
- Fructose intolerance
- Glucose malabsorption

Fat metabolism disorders

- Hypertriglyceridemia
- Hyperlipidemia
- Fatty acid oxidation defects

Vitamin disorders

- Biotinidase deficiency

Trace elements

- Metal metabolism disorders:
    - Hemochromatosis
    - Wilson's disease
    - Menkes disease

Specific disorders are suggested by signs as listed below

- Vomiting and acidosis after starting on breast milk or formula (amino acid or carbohydrate metabolism).
- Unusual odor of urine or sweat (e.g. burnt sugar smell in maple syrup urine disease)
- Hepatosplenomegaly (accumulation of metabolites within the cells of liver and spleen)
- Mental retardation
    - Brain atrophy due to harmful circulating metabolites such as Phenylketonuria (PKU)
    - Enlarged brain due to inability to metabolize intracellular substances
- Severe acidosis with high anion gap (abnormal metabolites of amino acid and organic acid metabolism)
- Hyperammonemia (urea cycle and organic acid disorders)

Diagnosis

- Complete blood count with differential
- Urinalysis
- Blood gases
- Serum electrolytes
- Blood glucose
- Plasma ammonia
- Urine reducing substances
- Urine ketones if acidosis or hypoglycemia present
- Plasma and urine amino acids, quantitative
- Urine organic acids
- Plasma lactate
- Most important laboratory finding associated with inborn errors of metabolism presenting with an acute encephalopathy is hyperammonemia (urea cycle defects, organic acidemias).
- The second important laboratory finding of many of the inborn errors of metabolism is metabolic acidosis with an increased anion gap (measured by arterial blood gases or serum electrolytes and bicarbonate).
- Plasma lactate often is elevated in organic acidemias.
- Hypoglycemia may be seen in infants with disorders of protein intolerance, disorders of carbohydrate metabolism or fatty acid oxidation. Most common inborn errors of metabolism associated with hypoglycemia are the hepatic Glycogen Storage Diseases (GSD).
- Common metabolic disease associated with jaundice is galactosemia.

GLYCOGEN STORAGE DISEASE

CASE

A 9-month-old boy presents with ***sweating*** and ***tachypnea***. On clinical examination, there is 5 cm ***hepatomegaly***. Random blood glucose is 40 mg/dL***(hypoglycemia)***. Liver biopsy confirms glycogen storage disease.

- Glycogen is a highly branched polymer of glucose that is stored in liver and muscle.
- Glycogen Storage Diseases (GSD) result from storage of glycogen in various organs.
- There is incomplete degradation of glycogen due to deficiency of various enzymes, which break down glycogen at various stages of its metabolism.
- Almost all of these conditions are autosomal recessive, except type VII that is X-lined.
- Clinical manifestations vary with different disorders.
- Signs and symptoms suggestive of glycogen storage disease may include:
    - Hypoglycemia
    - Seizures
    - Enlarged liver or kidneys
    - Lactic acidosis
    - Cardiomegaly
    - Hypotonia
    - Hyperlipemia
    - Developmental delay
    - Muscle weakness
    - Neurologic deterioration
    - Growth retardation
- Glycogen storage diseases fall into four categories.

Glycogen storage diseases predominantly affecting the liver

- These are glycogen storage disease types I, VI, and VIII.
- They have direct influence on blood glucose (hypoglycemia causing irritability, seizures or coma).
- In type I, symptoms and signs may be present at birth or appear in early infancy. There is protuberant abdomen, hepatomegaly, growth retardation, and typical doll facies.

Glycogen storage diseases predominantly affecting skeletal muscle

- These are glycogen storage disease types V and VII.
- They affect the ability to do anaerobic work.
- They present with hypotonia, muscle cramps, muscle pain, easy fatigability, and rarely with myoglobinuria.

Glycogen storage disease affecting both liver and muscle

- This is glycogen storage disease type III.
- It indirectly influences both blood glucose and muscle metabolism.

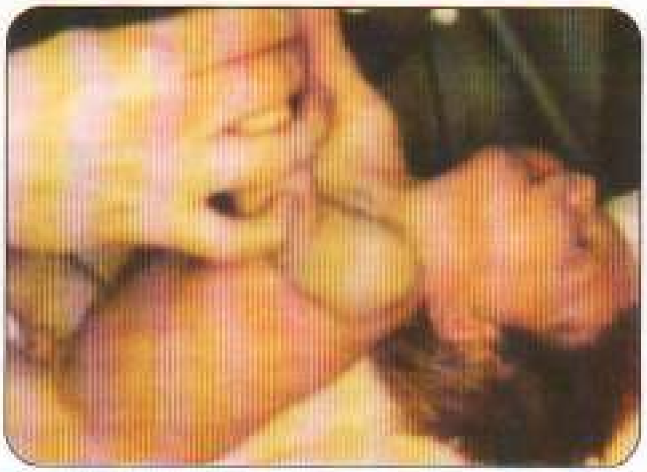


Figure 20.2: Floppy baby head lag Pompe disease.

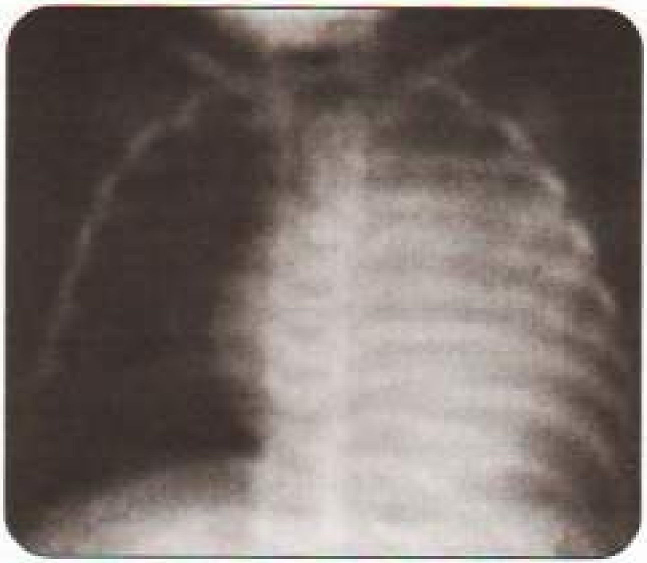


Figure 20.3: Cardiomegaly in Pompe disease.

Glycogen storage diseases affecting various tissues

- These are glycogen storage diseases types II and IV.
- They have no direct effect on blood glucose or on the ability to do anaerobic work.
- Type II (Pompe's disease) mainly affects the heart muscle. It present with signs and symptoms of heart failure, cardiomegaly, cyanosis or shock. On chest X-ray, heart is grossly enlarged.

Diagnosis

- Selection of investigations depends upon the type of glycogen storage disease suspected clinically.
- Precise diagnosis is by biochemical tests, such as:
  - Responsiveness of blood glucose to fasting and glucagon
  - Enzyme assays on leukocytes, liver, or muscle
- **Blood glucose level:** There is hypoglycemia in types involving liver.
- **Glucose tolerance test:** There is pre-diabetic type glucose tolerance curve in type I. Test dose of glucose is given orally in a dose of 1.5 gm/kg. Blood glucose shows abnormal high-rise and delayed fall.
- **Glucagon tolerance test:** If 1 mg IV glucagon is given, it raises blood glucose level 40–60% above fasting level in normal person but not in glycogen storage disease type I, where flat curve is obtained. The test can also be performed by SC adrenaline 0.3–0.5 ml.
- **Liver biopsy:** It is confirmatory test in glycogen storage disease involving liver. Liver glycogen is more than 5% of its weight. There are ballooned hepatocytes due to the accumulation of glycogen. Enzyme study shows either absent or reduced glucose-6-phosphatase activity in type I.
- **Glycogen content** in the affected tissues is raised.
- **CPK** (Creatinine Phosphokinase) may be raised in the glycogen storage disease affecting skeletal muscle.
- Glycogen storage disease involving muscles can be assessed by:
  - Electromyography
  - Measurement of the response of blood lactate to ischemic exercise (normally there is a brisk rise but there is little change in type V)
  - Muscle biopsy
- In some cases, there may be low pH, raised blood lactic acid and ketone bodies in blood and urine, and raised phospholipids and cholesterol.

Differential diagnosis

- The glycogen storage disease is included in the differential diagnosis of hypoglycemia and of hepatomegaly.

Management

- Management of hepatic glycogen storage disease is mainly by maintaining satisfactory blood glucose levels, and preventing lactic acidosis.
- Type I requires nocturnal intra-gastric feedings of glucose and frequent snacks.
- No specific treatment is available for the glycogen storage disease of muscle that impairs ischemic exercise.
- Liver transplantation is an option for severe hepatic glycogen storage disease.

MUCOPOLYSACCHARIDOSES

CASE

A 5-year-old child has ***coarse facial features*** (thick lips and a large tongue). He has ***progressive loss of developmental milestones*** and severe ***mental retardation***. Lumbosacral kyphosis is prominent. He has ***hazy corneas***. Examination urine reveals dermatan and heparansulfate.

- The mucopolysaccharidosis is associated with lysosomal accumulation of partially degraded acid Mucopolysaccharides (MPSs).
- MPSs are large molecules composed of repeated sulfatedhexuronate or hexosamine disaccharide units attached to a protein core. Normally, MPSs are degraded by acid hydrolases. Deficiency of a specific hydrolase results in partial degradation of the molecule and lysosomal storage of the residual fragments.
- Depending on the deficiency of specific hydrolases, degradation of any one of the following may be affected alone or in combination:
  - **Heparansulfate:** Disorders associated with heparansulfate storage mainly affect central nervous system and causes progressive mental retardation.
  - **Dermatansulfate:** Disorders associated with dermatansulfate storage have visceral and bone involvement.
  - **Keratansulfate:** Disorders associated with keratan storage have bone involvement.
  - **Chondroitin sulfate:**
- The age of onset, severity, and pattern of clinical and radiographic findings help to distinguish between the various types of mucopolysaccharidosis.
- In some cases, urinary testing of MPS is helpful for diagnosis. Diagnosis is made on the basis of testing specific lysosomal hydrolases. Demonstration of deficient activity of a specific lysosomal hydrolase is done in serum or leukocytes. In some disorders, cultured skin fibroblasts are required.

Radiographic findings

- There is a distinct pattern on radiographs called dysostosis multiplex.
- Skull is enlarged and elongated (dolichocephaly), and calvarium is thick. Sella is J-wooden-shoe-shaped or boot-shaped.
- Vertebral bodies in the lower thoracic and upper lumbar areas have a "beaking" of the anterior inferior surface caused by hypoplasia of their anterio-superior areas. A dorsal kyphosis, or gibbus deformity, develops.

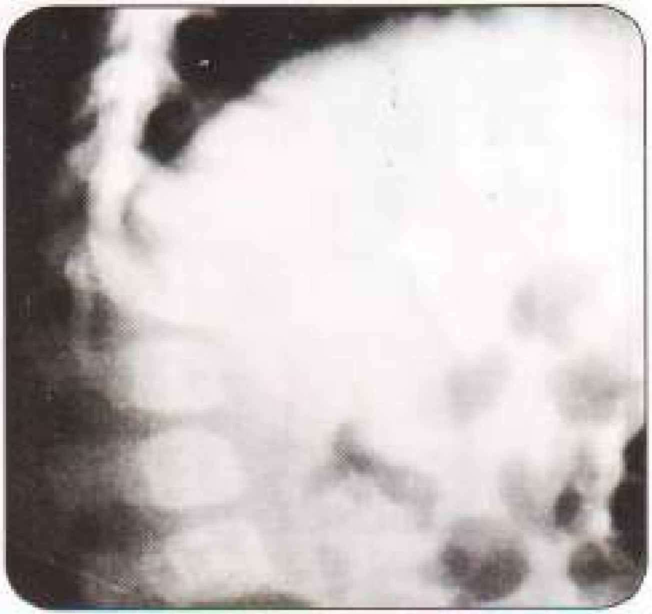


Figure 20.4: Vertebral bodies in a case of MPS showing characteristic findings.

- Ribs are thickened, except where they join the spine. They have an oar-shaped appearance.
- Distal humerus and ulna may show an abnormal angulation (Madelung's deformity).
- Pelvis may have flaring of the iliac bones, shallow acetabular areas, and progressive coxavalga.
- Long bones become shortened and thickened. There are signs of expansion of the medullary cavity.
- There may be hypoplasia of the odontoid process.
- Metacarpals have a proximal narrowing with distal widening (bullet shape appearance).

HURLER SYNDROME (MPSI)

- In Hurler syndrome, there is deficiency of α-L-iduronidase. There is excessive storage of heparan and dermatansulfates.
- It is inherited as an autosomal recessive trait. It occurs in about 1:100,000 births.
- It is the most severe type of MPSs.
- Children with Hurler syndrome appear normal at birth.

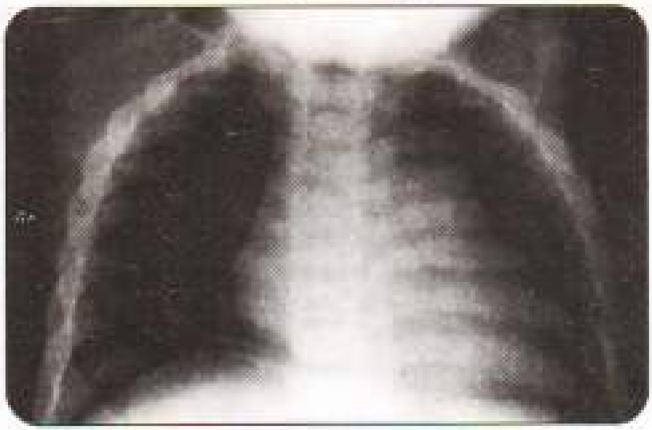


Figure 20.5: Flaring of ribs.

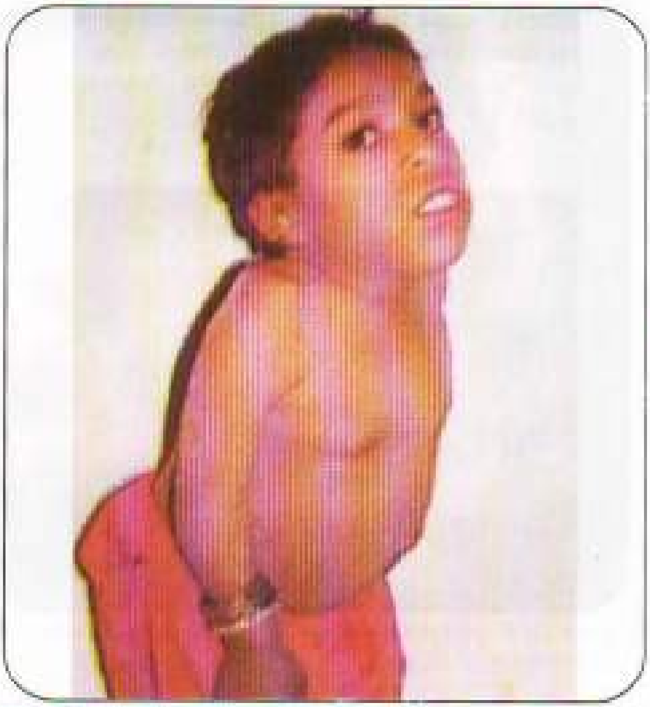


Figure 20.6: Mucopolysaccharidosis

- Features appear at about 6–12 months of age.
- There is gradual coarsening and prominence of the facial features. There is flattening of the mid-facial areas with depressed nasal bridge, frontal bossing, and anteverted nares.
- Cornea is cloudy.
- There is gradual gingival hyperplasia and thickening of the alveolar ridge. Dental eruption is delayed.
- There may be deafness.
- Respiratory involvement is due to thickening of the soft tissues in the nose and pharynx. There is persistent rhinorrhea or noisy breathing. Sleep apnea and corpulmonale is due to gradual upper airway obstruction.
- Cardiac lesions occur between ages of 2–5 years. These include thickened valve leaflets, pseudo-artheromatosis of the coronary arteries, cardiomyopathy, and congestive heart failure.
- During the first year of life, hepatosplenomegaly develops.
- There is also umbilical and inguinal hernia.
- Bone growth is delayed. There is minimal linear growth after 2–3 years of age.
- Other features are gibbus deformity, dorsolumbar kyphosis, large dolichocephalic head with prominent frontal areas and suture lines, joint stiffness, carpal tunnel syndrome, thickening of the meninges with hydrocephalus, and decreased compliance of the thoracic cage.
- Psychomotor development regresses gradually after 1–2 years.
- Due to joint stiffness and bony involvement, there is limitation of physical activity. There are contractures of the lower limbs and stiff hands become claw-like.
- Radiograph shows dysostosismutiplex.
- Hurler syndrome is confirmed by demonstrating deficient activity of ∝-L-iduronidase in leukocytes or cultured skin fibroblasts.
- Prenatal diagnosis is possible with chorionic villi sampling and cultured amniotic fluid cells.

HUNTER SYNDROME: (MPS II)

- There is deficient activity of idurono-sulfatesulfatase.
- There is storage of heparan and dermatansulfate.
- It is inherited as an X-linked trait.
- There are two forms of Hunter's syndrome: severe (type A) and mild (type B).
- Severe form has the same clinical features as those of Hurler syndrome except that the onset is between 1–2 years of age. Course of the disease is slower. There is no corneal clouding. Deafness is common.
- Skin lesions (ivory raised papules) are present on the upper back and on the lateral upper arms and thighs.
- Patients in severe form commonly survive up to second or third decades.
- Patients in milder type have normal intelligence. They survive into the sixth or seventh decade of life.
- Deficient activity of iduronosulfatesulfatase is noted in serum, leukocytes, and cultured skin fibroblasts.
- Prenatal diagnosis is possible by chorionic villi sampling and cultured amniotic fluid cells.

MORQUIO SYNDROME: (MPS IV)

- There is keratansulfate and chondroitin 6-sulfate storage.
- In type A, there is deficient activity of N-acetylgalactosamine-6-sulfate sulfatase (galactose-6-sulfatase).
- In type B, there is deficient β-galactosidase.
- It is inherited as autosomal recessive trait.
- Mental retardation is usually not present.
- Major clinical feature is skeletal involvement. Onset of short stature and joint laxity occurs at about 1 year of age. There is shortening of the trunk and neck, flaring of the ribs, prominence of the sternum (pectuscarinatum), genu valgum, and enlargement and instability of the joints.
- There is mild corneal clouding and hepatosplenomegaly.
- In type A, there is enamel hypoplasia. It is not present in type B.
- Progressive hearing loss is present.
- Due to skeletal involvement, there are cardiorespiratory problems, especially valvular heart disease.

- There is acute or chronic cervical myelopathy, severe hypoplasia of the odontoid process, and atlantoaxial subluxation.
- Patients with severe form have minimal linear growth after 6–7 years of age. They die of cardiorespiratory compromise in their third or fourth decade. Patients with mild cases survive up to seventh decade.
- By 2 years of age, radiographic findings are evident. These include flattening of the vertebral bodies (platyspondyly), hypoplasia of the odontoid process, irregular metaphyses, shortening of the long bones, and findings similar to those of Hurler syndrome in the wrists and metacarpals.
- Early in the disease, there is keratansulfaturia.
- Disease is confirmed by demonstration of the enzyme deficiencies in cultured skin fibroblasts.

GALACTOSEMIA

CASE

A 6-day-old baby presents with ***poor feeding*** and ***vomiting***. Liver function tests show hyperbilirubinemia. There is hypoglycemia. Ophthalmoscopic examination shows a central ***cataract***. Blood cultures are positive for Escherichia coli. He does well on intravenous fluids. When begun on routine infant formula, his symptoms return.

Definition

- Galactosemia is the inability of the body to use (metabolize) the simple sugar galactose, causing the accumulation of galactose 1-phosphate in the body.
- This causes damage to the liver, central nervous system, and other body systems.

Etiology and risk factors

- Galactosemia is an inherited enzyme disorder (transmitted as an autosomal recessive trait.
- There are 3 forms of the disease:
  - Galactose-1-phosphate uridyltransferase deficiency (classic galactosemia, the most common and most severe form)
  - Deficiency of galactose kinase
  - Deficiency of galactose-6-phosphate epimerase
- People with galactosemia are unable to fully break down the simple sugar galactose. Galactose makes up half of lactose, the sugar found in milk.
- If an infant with galactosemia is given milk, derivatives of galactose build up in the infant's system, causing damage to the liver, brain, kidneys, and eyes.
- Individuals with galactosemia cannot tolerate any form of milk (human or animal) and must be carefully watched for intake of other galactose-containing food.
- Exposure to milk products may result in liver damage, mental retardation, cataract formation, and kidney failure.
- After drinking milk for a few days, a newborn with galactosemia will refuse to eat and develop jaundice, vomiting, lethargy, irritability, and convulsions. The liver will be enlarged and the blood sugar may be low.
- Continued feeding of milk products to the infant leads to cirrhosis of the liver, cataract formation in the eye (which may result in partial blindness), and mental retardation.

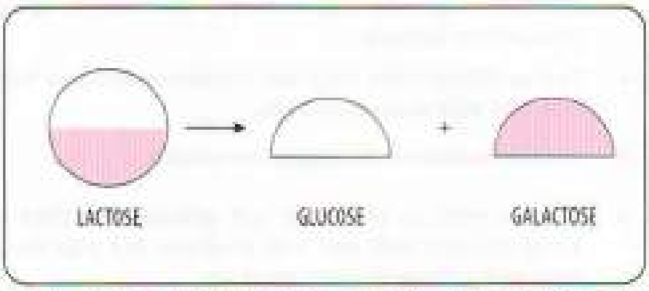


Figure 20.7: Hydrolyzation of lactose into glucose and galactose

Clinical findings

- Jaundice
- Vomiting
- Poor feeding (baby refusing to drink milk-containing formula)
- Poor weight gain
- Lethargy
- Irritability
- Convulsions
- Hepatomegaly
- Hypoglycemia
- Aminoaciduria (amino acids are present in the urine and/or blood plasma)
- Cirrhosis
- Ascites
- Mental retardation
- Cataract formation

Differential diagnosis

- Rubella infection
- Sepsis of the newborn
- Hereditary fructose intolerance, urea cycle abnormalities produce neonatal liver dysfunction and emesis

Diagnosis

- Prenatal diagnosis by direct measurement of the enzyme galactose-1-phosphate uridyltransferase.
- The presence of "reducing substances" in the infant's urine with normal or low blood sugar while the infant is being fed breast milk or a formula containing lactose. A simple test on the urine indicates the presence of a reducing substance, and a specific enzymatic study on the urine can prove the substance to be galactose.
- Presence of ketones in urine

- Measurement of enzyme activity in the red blood cells
- Blood culture for bacterial infection (*E. coli sepsis*)

Management

- Once the disease is recognized, treatment consists of strictly avoiding all milk and milk-containing products.
- The infant can be fed with soy formula, or other lactose-free formula.
- The condition is life-long and requires avoidance from milk and milk products for life.
- Calcium supplements are recommended.
- Parents need to take care and educate the child to avoid not only milk and milk products, but also those food that contain dry milk products.

Prognosis

- If diagnosis is made early and milk products are strictly avoided, the prognosis is for a relatively normal life.
- Despite strict avoidance of galactose, mild intellectual impairment may still develop.

Complications

- Cataracts
- Cirrhosis
- Severe infection with bacteria (*E. coli sepsis*)
- Delayed speech development
- Severe mental retardation
- Irregular menstrual cycles, decreased function of ovaries, leading to ovarian failure
- Tremors and uncontrollable motor functions
- Death (if diet is not adhered to)

PHENYLKETONURIA

CASE

A 3 months old infant presents with irritability and vomiting. He was born with fair hair, blue eyes, and fair skin. On examination, he has an eczematous rash. He has a musty, mousy odor.

Definition

- Phenylketonuria (PKU) is a genetic disorder that is characterized by an inability of the body to utilize the essential amino acid, phenylalanine.
- In **classic PKU,** the enzyme that breaks down phenylalanine, phenylalanine hydroxylase, is completely or nearly completely deficient.
- This enzyme normally converts phenylalanine to another amino acid, tyrosine. Without this enzyme, pheny-lalanine and its breakdown chemicals from other enzyme routes, accumulate in the blood and body tissues.
- A normal blood phenylalanine level is about 1 mg/dl. In classic PKU, levels may range from 6 to 80 mg/dl, but are usually greater than 30 mg/dl.
- Chronically high levels of phenylalanine and some of its breakdown products can cause significant brain problems.

Inheritance

- PKU is autosomal recessive disorder.
- Carriers do not have symptoms of the disorder.

Clinical findings

- Infants with PKU appear normal at birth.
- Many have blue eyes and fairer (blond) hair and skin than other family members.
- About 50% of untreated infants have early symptoms, such as vomiting, irritability, an eczema-like rash, and a mousy odor to the urine.
- Some may also have subtle signs of nervous system function problems, such as increased muscle tone, and increased muscle tendon reflexes.

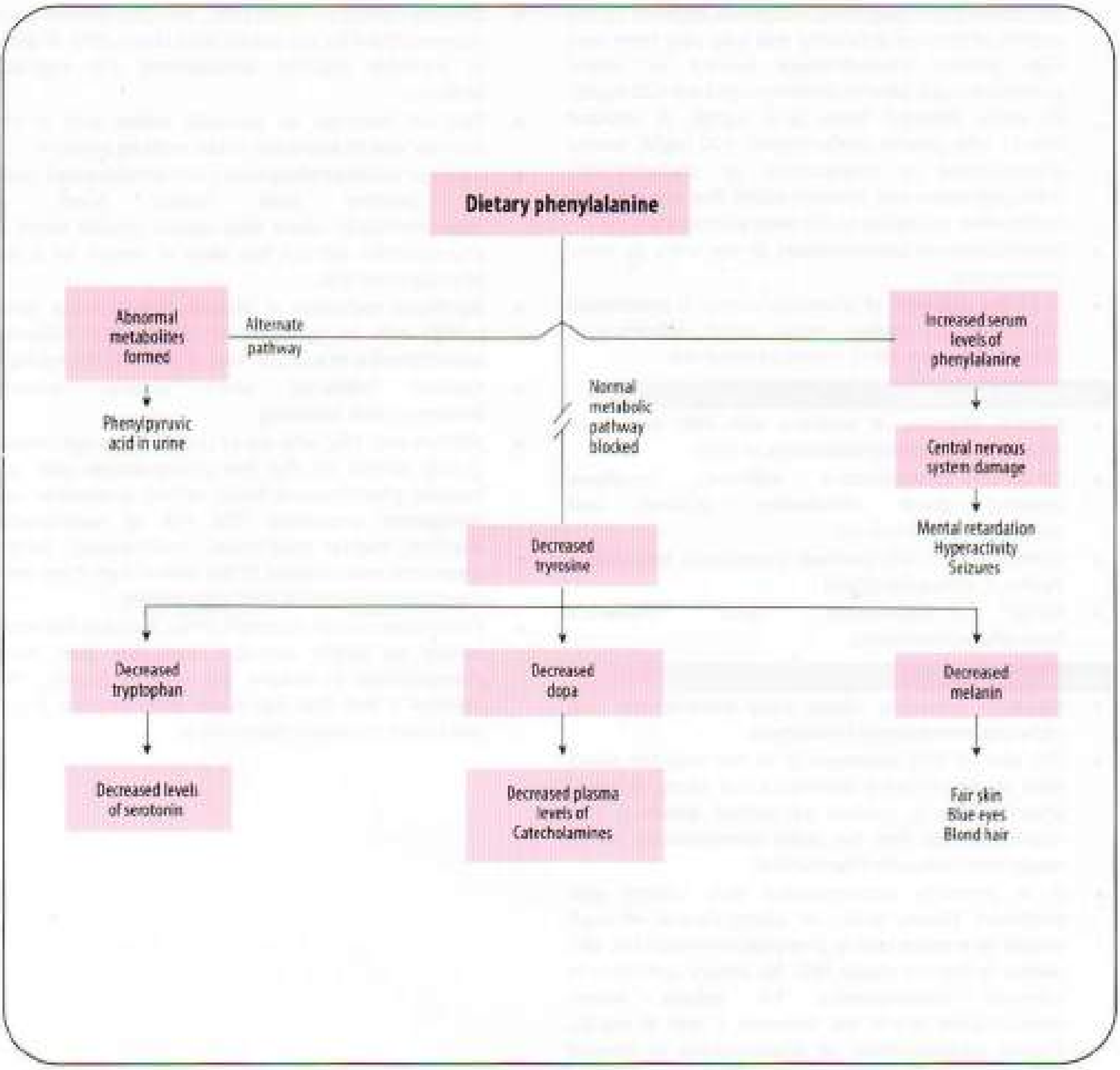

Dietary phenylalanine
Abnormal metabolites formed
Alternate pathway
Phenylpyruvic acid in urine
Increased serum levels of phenylalanine
Normal metabolic pathway blocked
Central nervous system damage
Mental retardation
Hyperactivity
Seizures
Decreased tyrosine
Decreased tryptophan
Decreased dopa
Decreased melanin
Decreased levels of serotonin
Decreased plasma levels of Catecholamines
Fair skin
Blue eyes
Blond hair

Figure 20.8 : Inheritance of phenylketonuria.

- Later, severe brain problems occur, such as mental retardation and seizures.
- Other commonly noted features in untreated children include: microcephaly (small head), prominent cheek and upper jawbones with widely spaced teeth, poor development of tooth enamel, and decreased body growth.

Diagnosis

- Detection of a raised phenylalanine level on neonatal screening.Newborn screening is highly reliable.
- In infants with positive results from the screen for hyperphenylalaninemia, diagnosis should be confirmed by quantitative measurement of plasma phenylalanine.
- Blood phenylalanine in affected infants with PKU may rise to diagnostic levels as early as 4 hours after birth even in the absence of protein feeding. It is recommended that the blood for screening be obtained in the first 24–48 hours of life after feeding protein to reduce the possibility of false negative results, especially in the milder forms of the condition.

- The severity of hyperphenylalaninemia depends on the degree of enzyme deficiency and may vary from very high plasma concentrations (severe or classic phenylketonuria plasma concentrations are >20 mg/dl) to mildly elevated levels (2–6 mg/dl). In affected infants with plasma concentrations >20 mg/dl, excess phenylalanine is metabolized to phenylketones (phenylpyruvate and phenylacetate) that are excreted in the urine, giving rise to the term phenylketonuria.
- Identification of phenylketones in the urine by ferric chloride test.
- Once the diagnosis of phenylalaninemia is established (confirmed on plasma amino acids) deficiency of cofactor biopterin (BH_4) should be ruled out.

Differential diagnosis

- Normal offspring of mothers with PKU may have transient hyperphenylalaninemia at birth.
- Dihydropteridinereductase deficiency (produces elevated pterin metabolites, seizures, and psychomotor regression).
- Defects in biopterin synthesis (myoclonus, tetraplegia, dystonia, oculogyric crises).
- Benign tyrosinemia with moderate hyperphenylalaninemia.

Management

- Newborn screening allows early identification and early implementation of treatment.
- The goal of PKU treatment is to maintain the blood level of phenylalanine between 2 and 10 mg/dl. Some phenylalanine is needed for normal growth. This requires a diet that has some phenylalanine but in much lower amounts than normal.
- It is generally recommended that infants with persistent plasma levels of phenylalanine >6 mg/l should be treated with a phenylalanine-restricted diet similar to that for classic PKU. No dietary restriction is currently recommended for infants whose phenylalanine levels are between 2 and 6 mg/dL. Plasma concentrations of phenylalanine in treated patients should be maintained as close to normal as possible.
- Over treatment is avoided as phenylalanine is not synthesized by the body.

- High protein food, such as: meat, fish, poultry, eggs, cheese, milk, dried beans, and peas are avoided.
- Instead, measured amounts of cereals, starches, fruits, and vegetables, along with a milk substitute are usually recommended.
- Phenylalanine free formulas are available now.
- Dietary therapy is most effective when started at birth. But it may also improve hyperactivity, irritability, and distractibility if started later in life.
- Lifelong dietary restriction of phenylalanine is recommended for individuals with classic PKU, in order to promote maximal development and cognitive abilities.
- Tyrosine becomes an essential amino acid in this disorder and its adequate intake must be ensured.
- Cofactor tetrahydrobiopterin (BH_4) administered orally to patients with milder forms of hyperphenylalaninemia may reduce plasma levels of phenylalanine without the need to remain on a low phenylalanine diet.
- Significant reduction in plasma phenylalanine levels (>30%) can be achieved in classic PKU following administration of a single dose of oral BH_4 (10 mg/kg).
- Medical follow-up often involves periodic developmental screening.
- Women with PKU who are of child bearing age, should closely adhere to the low phenylalanine diet and monitor phenylalanine levels before conception and throughout pregnancy. The risk of spontaneous abortion, mental retardation, microcephaly, and/or congenital heart disease in the child is high if mother's blood phenylalanine is poorly controlled.
- Phenylalanine is an essential amino acid and therefore cannot be totally excluded from the diet. Some phenylalanine is needed for normal growth. This requires a diet that has some phenylalanine but in much lower amounts than normal.

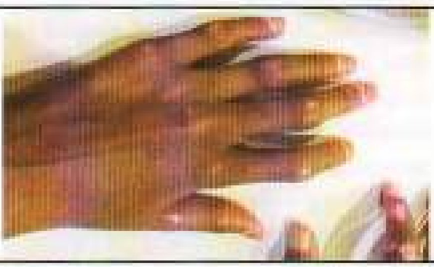
CHAPTER 21

Rheumatic Diseases

JUVENILE IDIOPATHIC ARTHRITIS (JIA)

CASE

A 4-year-old girl presents with a ***limp*** and a ***swollen left knee and fingers***. She complains of ***decreasing visual acuity*** and a slight feeling of discomfort in both eyes. She has ***spindle-shaped swelling*** of finger joints. Ophthalmic examination is abnormal (***iridocyclitis***). Antinuclear Antibody (***ANA***) is ***positive***.



Rheumatoid Arthritis

- It is one of the most common rheumatic diseases of children. It is characterized by an idiopathic synovitis of the peripheral joints, associated with soft tissue swelling and effusion.

Definition

- A chronic arthritis that persists for a minimum of 6 consecutive weeks in one or more joints, commencing before the age of 16 years and after active exclusion of other causes.

Criteria for the classification of juvenile idiopathic arthritis

- Age at onset: <16 years.
- Arthritis in ≥1 joint (swelling or effusion, or the presence of two or more of the following signs:
  - Limitation of range of motion
  - Tenderness or pain on motion
  - Increased heat
- Duration of disease: ≥6 weeks
- Onset type defined by type of articular involvement in the 1st 6 months after onset:
  - Polyarthritis: ≥5 inflamed joints
  - Oligoarthritis: ≤4 inflamed joints
  - Systemic-onset disease: Arthritis with rash and a characteristic quotidian fever
- Exclusion of other forms of juvenile arthritis

Etiology

- Two events are considered:
  - Immunogenetic susceptibility
  - Environmental triggers
- Certain viruses like parvovirus B19, rubella, and EBV may be responsible for JIA.

Epidemiology

- 1:1000 children under 16 years of age

Pathogenesis

- Synovitis of JIA is characterized by villous hypertrophy and hyperplasia with edema of subsynovial tissue.
- Infiltration of mononuclear and plasma cells and pannus formation occur in advanced disease and results in progressive erosion of articular cartilage and bone.

Classification

- Systemic onset disease
- Poly-articular onset
  - Rheumatoid factor negative
  - Rheumatoid factor positive
- Oligo-articular onset

Systemic onset disease

Arthritis in ≥1 joint with, or preceded by, fever of at least 2 weeks in duration that is documented to be daily (quotidian) for at least 3 days and accompanied by ≥1 of the following:

- Evanescent (nonfixed) erythematous rash
- Generalized lymph node enlargement
- Hepatomegaly or splenomegaly or both
- Serositis

Diagnosis

- There is no diagnostic test for JIA.
- ESR is high.
- Hemoglobin is low. There is normochromic normocytic anemia.
- White blood cell count is raised (neutrophil leucocytosis).
- Platelets are raised (>400 x 10^9/L).
- In oligoarticular JIA, CBC and platelets are normal.
- IgM rheumatoid factor is negative but may be positive in polyarticular onset disease.
- Anti-Nuclear Antibodies (ANA) are negative but are occasionally positive in polyarticular disease and frequently positive in oligoarticular disease.
- HLA–DR 4 is frequently present in RF-positive polyarticular disease and HLA–A2, DR5 and DR8 are present in oligoarticular disease.
- Radiographically, there are early changes of affected joints.

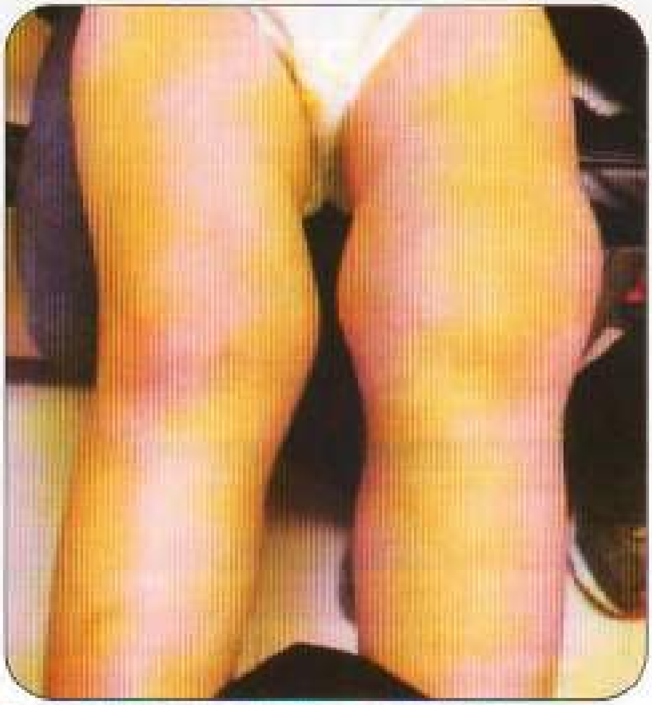


Figure 21.1: Knee joint swelling in a child (JIA).

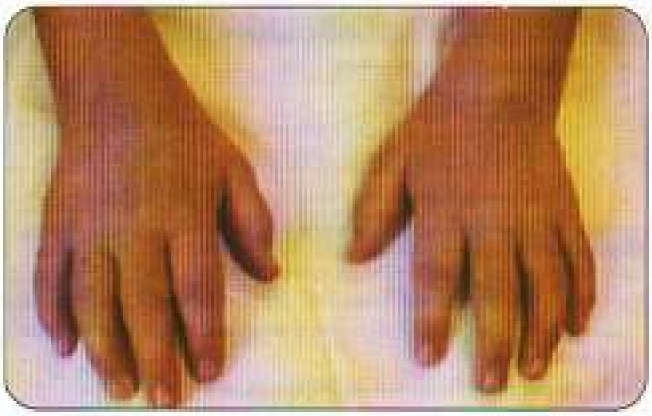


Figure 21.2: Wrist joint swelling in JIA.

Differential diagnosis

- Traumatic joint injury
- Reactive arthritides (Henoch-Schönleinpurpura, reactive arthritis, toxic synovitis of the hip, viral-associated synovitis)
- Acute rheumatic fever is characterized by exquisite joint pain and tenderness, a remittent fever, and polyarthritis that is usually migratory
- Acute joint infections
- Collagen-vascular disease (systemic lupus erythematous, dermatomyositis)
- Neoplastic disease (leukemia, lymphoma, neuroblastoma, bone and joint tumors)
- Autoimmune hepatitis can be associated with an acute arthritis.
- Monarticular arthritis unresponsive to anti-inflammatory treatment may be the result of chronic mycobacterial or other infection. Diagnosis is often established only by synovial biopsy.
- Joint pain and swelling of a single joint suggests trauma or infection; correlation with history, laboratory, and radiologic findings helps exclude these possibilities.

Management

- The main objectives of treatment are to:
  - Restore function
  - Relieve pain
  - Maintain joint motion

Physiotherapy

- Physiotherapy is important to maintain joint's mobility and muscle function. Range of motion and muscle strengthening exercise should be taught.
- Bed rest is not needed except in the most acute stage.

Nonsteroidal anti-inflammatory drugs

- Nonsteroidal Anti-inflammatory Drugs (NSAIDs) to control pain, inflammation and fever.
  - Naproxen 15 mg/kg/day PO divided bid (maximum dose 500 mg bid).
  - Ibuprofen 40 mg/kg/day PO divided tid (maximum dose 800 mg tid).
  - Meloxicam 0.125 mg/kg PO once daily (maximum dose 15 mg daily).

Disease-modifying anti-rheumatic drugs

- Methotrexate is the second-line medication of choice especially for arthritis. Symptomatic response usually occurs within 3–4 weeks. Dose is 0.5–1 mg/kg PO or SC weekly (maximum dose 25 mg/week) as a single dose.
- Sulfasalazine initial dose is 12.5 mg/kg PO daily. Increase by 10 mg/kg/day.
- Anti–tumor necrosis factor-α
  - Etanercept 0.8 mg/kg SC weekly or 0.4 mg/kg SC twice weekly (maximum dose 50 mg/week).
  - Infliximab 3–10 mg/kg IV q 4–8week.

Other measures

- Corticosteroids are used in severe disease, either pulsed intravenous, single daily dose or given on alternate days.
- Splinting is used to prevent deformity.
- Surgical intervention such as replacement arthoplasties is often required.
- Frequent ophthalmological assessment (for 3–6 months) is needed to prevent and treat iridocyclitis.

Prognosis

- There may be exacerbations and remissions.
- There may be alteration in growth of affected limb.
- The younger the age of onset, the greater the risk of poor growth.

- Iridocyclitis is bilateral in 2/3rd cases. Its prognosis depends on early detection and good management.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

CASE

A 12-year-old female presents with intermittent ***fever***, ***weight loss*** and ***joint tenderness*** for 2 months. There is facial erythema on the cheeks and nasolabial folds (***a butterfly rash***). There are several ***oral ulcers***. Liver is palpable 3 cm below the costal margin. Urine examination shows microscopic ***hematuria*** and ***proteinuria***. Laboratory data shows a ***positive antinuclear antibody test*** and low C3 and C4 levels.

- SLE is a chronic autoimmune disease characterized by:
  - Multisystem inflammation
  - The presence of circulating autoantibodies directed against self-antigens

Epidemiology

- Its prevalence in children is 1–6/100,000.
- It occurs more frequently in girls 2.5:1 before puberty and 9:1 during reproductive years.

Etiology

- The cause of SLE remains unknown, although many observations suggest a role for genetic, hormonal, immunologic, and environmental factors.
- The hallmark is autoantibody production against many self antigens particularly DNA as well as other nuclear antigen.

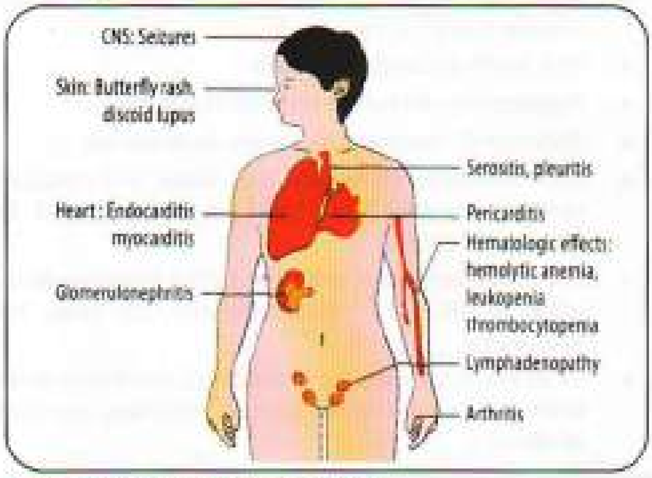

CNS: Seizures
Skin: Butterfly rash, discoid lupus
Heart : Endocarditis myocaditis
Glomerulonephritis
Serositis, pleurtis
Pericarditis
Hematologic effects: hemolytic anenia, leukopenia thrombocytopenia
Lymphadenopathy
Arthritis

Figure 21.3: Clinical features of SLE.

Pathogenesis

- Its main cause is formation of auto-antibodies directed against self-antigen.
- SLE skin cells get damaged by UV light causing cell necrosis or apoptosis and prolong exposure of nucleic acid in the blood leads to B-cell autoantibody production. This leads to complement activation and tissue damage.
- Antibodies to double-stranded DNA can deposit in glomeruli causing glomerulonephritis.

Table 21.1: Revised criteria for the classification of SLE.

A person shall be said to have SLE if any four or more of 11 criteria are present:

- **Malar rash**
- **Discoid rash**
- **Photosensitivity**
- **Oral or nasal ulcers**
- **Arthritis**
  - Nonerosive, ≥2 joints
- **Serositis**
  - Pleuritis, pericarditis or peritonitis
- **Renal manifestations**
  - Consistent renal biopsy
  - Persistent proteinuria or renal casts
- **Seizure or psychosis**
- **Hematologic manifestations**
  - Hemolyticanemia
  - Leukopenia (<4,000 leukocytes/mm^3)
  - Lymphopenia (<1,500 leukocytes/mm^3)
  - Thrombocytopenia (<100,000 thrombocytes/mm^3)
- **Immunologic abnormalities**
  - Positive anti–double-stranded or anti-Smith antibody
  - False-positive rapid plasma regain test result, positive lupus
    - Anticoagulant test result or elevated anticardiolipin.
    - Immunoglobulin (Ig) G or IgM antibody
- **Positive antinuclear antibody test result**

- Patients with type I interferon signature produce high levels of interferon- ∝ promoting auto-reactive B-and T-cells and loss of self-tolerance.
- There is increased number of abnormal T-cells and decreased number and function of T-regulatory cells resulting in an increased autoreactivity.

Clinical findings

The symptoms depend on the organ involved with immune complex deposition.

- General malaise
- Weakness
- Anorexia
- Weight loss
- In arthralgia or arthritis joint symptoms are the most common presenting feature.
- Myalgia and/or myositis
- Fever

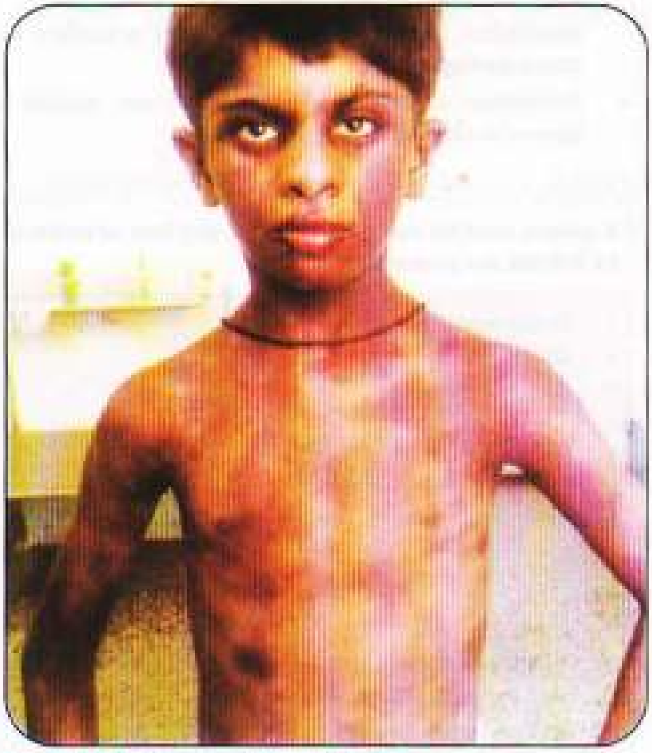


Figure 21.4: Characteristic rash in SLE.

- Muco-cutaneous lesions:
    - Malar rash
    - Popular, vesicular or purpuric lesions
    - Vasculitic skin lesions
    - Alopecia
    - Oral ulcers
    - Photosensitivity
- Renal disease: It is often progressive and is the leading cause of death among patients with SLE
- Pulmonary disease (pleuritis, interstitial infiltrations)
- Cardiac disease (periarditis, myocarditis, Libman-Sacks endocarditis)
- CNS disease (seizures, headache, psychosis)
- Cerebral disease (blurred vision, chorea, and transverse myelitis)
- Gastrointestinal disease (hepatosplenomegaly, mesenteric arteritis, inflammatory bowel disease)
- Eye disease (retinitis, episcleritis, iritis)
- Raynaud's phenomenon

Differential diagnosis

- Systemic-onset juvenile rheumatoid arthritis
- Acute poststreptococcal glomerulonephritis
- Acute rheumatic fever
- Infective endocarditis
- Leukemia
- Immune thrombocytopenic purpura
- Idiopathic hemolyticanemia

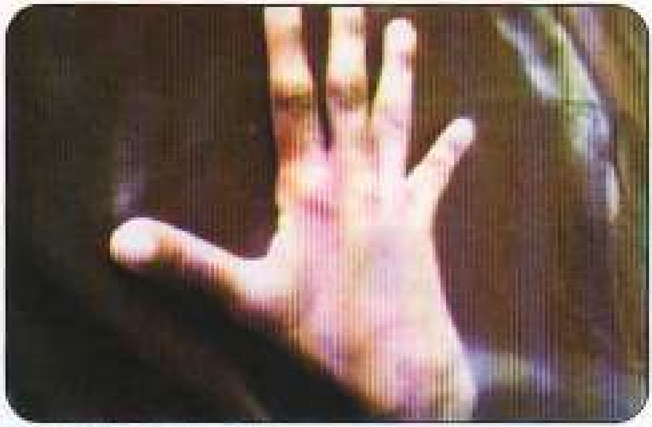


Figure 21.5: Hands in SLE.

- Viral infections
- Drug-induced lupus. The typical symptoms of fever, rash, and pleuropericardial disease typically abate with discontinuation of the drug.
- Collagen-vascular diseases and mixed connective tissue disease.

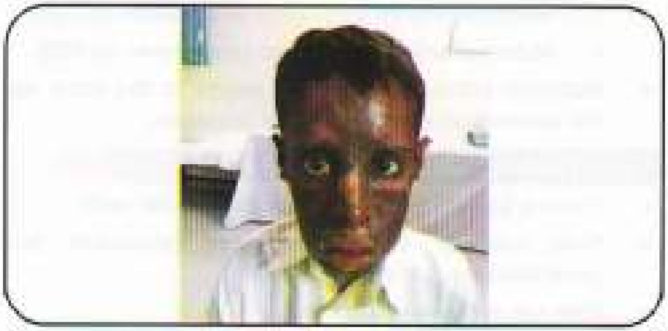
Diagnosis

- ESR–raised
- Hemoglobin–low (due to autoimmune hemolyticanemia or anemia of chronic disease)
- A low incidence of Coombs positivity
- Leucopenia (mainly lymphopenia)
- Thrombocytopenia in some cases
- IgM rheumatoid factor may be positive
- ANA strongly positive. A negative ANA test effectively excludes the diagnosis.
- Antibodies to double-stranded (ds) DNA are usually present in 2/3rd of cases.
- Anti-Smith antibody is positive
- Hypergamma-globulinemia is also frequent.
- Total complement and its components are low.
- Anti-cardiolipin antibodies and lupus anti-coagulant may be present. This shows an increased risk for thrombotic events.
- Renal involvement is indicated by the presence in the urine of red cells, white cells, red cell casts, and proteinuria.
- CT or MRI brain may show pathologic conditions of the brain in lupus cerebritis, such as infarction, vasculitis, or atrophy.

Management

- Treatment of SLE should be focused to the organ system involved so that toxicities of drugs may be minimized.
- Hydroxy-chloroquine (5–7 mg/kg/day orally) is used for skin and joint manifestations.
- NSAIDs are used for pleuritic pain or arthritis.

- Corticosteroids are the mainstay of treatment.
  - Patients with systemic disease are often started on 1–2 mg/kg/24 hours of oral prednisone in divided daily doses.
  - When complement levels increase to within the normal range, the dose is tapered to the lowest effective dose.
  - Severely ill patients may require pulse intravenous corticosteroid therapy (methyl prednisolone 30 mg/kg/dose, maximum 1 g/day, given over 60 min, for 3 days) followed by weekly pulses.
  - Adverse effects of corticosteroids include hypertension, gastritis, cataracts, osteopenia, and cushingoid body habitus.
- Sun exposure should be minimized and include use of a sunscreen.
- Cytotoxic drugs are used for serious intractable disease.
  - Azathioprine 2–3 mg/kg/day orally.
  - Cyclophosphamide 0.5–1 g/m^2 intravenous once a month.
  - Cyclophosphamide is used to treat vasculitis, pulmonary hemorrhage, and central nervous system involvement.
  - Azathioprine has been used to prevent renal disease progression. Adverse effects include secondary infections, gonadal dysfunction, and possibly increased risk of later malignancies.
  - Prepubertal children, compared with those who have entered puberty, may be at less risk for subsequent gonadal dysfunction from cytotoxic agents.
- Other interventions are being proposed for the treatment of lupus.
  - Methotrexate, cyclosporine, and mycophenolatemofetil are used as steroid-sparing agents.
  - Mycophenolate is an alternative to cyclophosphamide for some types of lupus nephritis.
  - Autologous stem cell and allogeneic bone marrow transplantation for patients with severe, persistent disease are undergoing clinical trials.
  - Biologic agents that target cytokine production are also being studied.
  - Other potential therapies include rituximab (anti-CD20 monoclonal antibody), as well as blockade of interleukin 6 (IL-6), T cell co-stimulatory molecules.
- The extent of renal involvement may be out of proportion to findings on urinalysis; renal biopsy for staging can help determine whether an immunosuppressive agent such as cyclophosphamide needs to be added to a corticosteroid regimen.
- Patients with thrombosis and antiphospholipid antibodies or a lupus anticoagulant should receive anticoagulant medication at least until lupus is in remission.
  - Low molecular weight heparin is the anticoagulant of choice; warfarin can also be used.
- Side effects of all therapies may be severe.
- SLE is a lifelong illness, and patients require monitoring indefinitely.



SLE rash on face

Complications

- The major causes of death in patients with lupus currently include:
  - Infection
  - Nephritis
  - Central nervous system disease
  - Pulmonary hemorrhage
  - Myocardial infarction
  - Persistent leukopenia
  - Anemia
  - Thrombocytopenia

Prognosis

- Course is highly variable.
- Prognosis depends mainly on the extent and severity of systemic involvement.
- There is high risk of morbidity and mortality. The 5 years survival rate is ~95%.
- Main causes of death are infectious complications (including bacterial endocarditis), myocardial infarction, atherosclerosis, malignancy, pulmonary fibrosis and renal failure.
- Meticulous monitoring is essential.

NEONATAL LUPUS

CASE

A newborn presents with ***petechiae***. Her vital signs are stable. Heart rate is 60 per minute (***bradycardia***) and a respiratory rate 40 per minute. There is hepatomegaly and an erythematous rash on the cheeks and the bridge of the nose. Mother has a history of systemic lupus erythematosis.

- Neonatal lupus is a rheumatic disorder manifested in the neonate.

Pathogenesis

- Neonatal lupus results from the passive transfer of maternal immunoglobulin G autoantibodies to the fetus.
- Main maternal antibodies are:

  - Maternal anti-Ro antibodies (also known as SSA).
  - Maternal anti-La antibodies (also known as SSB).
- Maternal autoantibodies gain access to the fetus via the placenta at the 16th week of gestation.

Clinical findings

- There is a characteristic annular or macular rash:
- Rash typically affects the face (especially the periorbital area), trunk and scalp.
- Rash can be present at birth.
- The rash typically appears within the first 6 weeks of life after exposure to ultraviolet light and lasts for about 3–4 months.
- Complications:
  - Cytopenias
  - Hepatitis
  - Congenital heart block. About 2% of offspring born to mothers with anti-Ro and anti-La antibodies develop congenital heart block.
- Conduction system abnormalities are:
  - Prolongation of the PR interval to complete heart block.
  - Development of progressive cardiomyopathy (in severe cases).
- The non-cardiac manifestations are usually reversible. Congenital heart block is permanent.

Diagnosis

- Fetal echocardiography:
  - Conduction system abnormalities can be detected in utero by fetal echocardiogram after 16 weeks of gestational age.
- Maternal anti-Ro or anti-La antibody

Management

- Following measures are used in pregnant women with anti-Ro or anti-La antibodies to prevent occurrence or progression of fetal cardiac abnormalities, including congenital heart block, endocardialfibroelastosis, and hydropsfetalis:
  - Corticosteroids (dexamethasone or betamethasone)
  - Intravenous immunoglobulin
  - Plasmapheresis
  - Hydroxychloroquine
  - Terbutaline (combined with steroids)
- Maternal treatment with hydroxychloroquine may provide effective prophylaxis against congenital heart block.
- Corticosteroids have some benefit in improving hydropsfetalis.
- All pregnant women with circulating anti-Ro or anti-La antibody are monitored by a regular fetal electrocardiography from 16 weeks of gestation until delivery.
- After birth treatments:
  - Conduction system abnormalities are treated with cardiac pacing.
  - Occasionally intravenous immunoglobulin and steroids are of benefit.
  - Severe cardiomyopathy may require cardiac transplantation.
  - Transient, non-cardiac manifestations are managed conservatively. Rash is treated with topical steroids.

Prognosis

- Neonatal lupus is not an ongoing immune dysregulation. But there is an increased risk for development of future autoimmune disease.
- If a mother has a previous child born with congenital heart block due to neonatal lupus, there is about 17% risk of recurrence with future pregnancies.
- With cardiac pacing, prognosis is excellent (if there is no cardiomyopathy).
- If conduction defect are not properly managed, affected children have exercise intolerance and arrhythmias leading to death.

HENOCH-SCHÖNLEIN PURPURA (HSP)

CASE

A 7-year-old boy presents with ***abdominal pain*** and a ***rash mainly on the back of his legs and buttocks***. On physical examination, there is generalized abdominal tenderness, tender swelling of both ankles and knees, and a rash that ***do not blanch when pressed***. A complete blood count and urine analysis are normal. Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and ***platelet counts are normal***. Blood urea and creatinine are also normal. Urinalysis shows hematuria and proteinuria. Stool is guaiac positive.

- It is the most common small vessel vasculitis syndrome in children.
- There is inflammation of small vessels and capillaries particularly those of the skin, gastrointestinal tract, and kidney.
- It may be preceded by infection, particularly hemolytic streptococci, staphylococcus aureus, mycoplasma and adenovirus (in the preceding 1–3 weeks).
- Onset is generally after the age of 3 years. There is a slight male predominance.

Pathogenesis

- The specific pathogenesis is unknown.

- The illness is considered to be an IgA-mediated vasculitis of small vessels.
- Immunofluorescence techniques show deposition of IgA and C3 in small vessels of skin and renal glomeruli.

Clinical findings

- HSP often follows an upper respiratory tract infection.

Palpable purpura (non-thrombocytopenic purpura)

- The most common and earliest symptom is palpable purpura (initially blanch on pressure). It results from extravasation of erythrocytes into the tissue surrounding the involved venules. Purpuricmacules, are usually present on the legs, feet and buttocks but the entire body may be involved. This progresses to large hemorrhages (palpable purpura) particularly over the elbows and knees.
- Localized areas of subcutaneous edema that affect the forehead, dorsa of hands and feet, periorbital areas, lips and scrotum.

Arthritis

- Arthritis and arthralgia are transient involving large joints.
- It is present in more than $^2/3$ of children with HSP.

Abdominal pain

- There is colicky abdominal pain (50%) and/or gastrointestinal bleeding (due to hemorrhage and edema primarily of the small intestine).
- More than half of patients have occult heme positive stools, diarrhea (with or without visible blood), or hematemesis.
- Intussusception may occur.

Renal involvement

- 25–50% have renal involvement, proteinuria, hematuria, hypertension, nephritis, nephrosis or acute renal failure.
- Testicular torsion may occur.
- Neurologic manifestations include cerebral hemorrhage, seizures, headaches and behavioral changes.

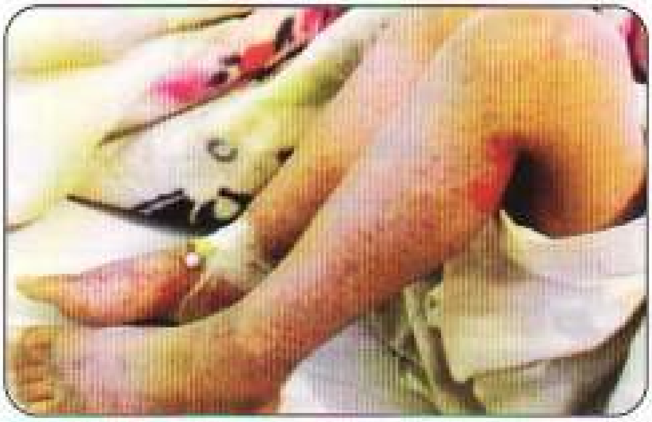


Figure 21.6 : Rash in HSP.

Diagnosis

- Routine laboratory tests are not specific or diagnostic.
- The diagnosis of HSP is clinical. It is often straightforward when the typical rash is present. However, in at least 25% of cases, the rash appears after other manifestations, making early diagnosis difficult.
- ESR normal or high
- Complete blood count is normal
- Anemia may be due to GIT blood loss
- Hematuria and/or proteinuria
- Blood coagulation studies are normal
- Abdominal ultrasonography to look for intussusception.
- Serum IgA is often raised.
- Stool examination may be positive for blood but melena is not present.
- Antistreptolysin O (ASO) titer is frequently raised and the throat culture is positive for group A β-hemolytic streptococci.
- Definitive diagnosis of vasculitis is confirmed by biopsy.
- Renal biopsy may show mesangial deposition of IgA, IgM, C3 and fibrin.

Complications

- Intussusception of the small intestine
- Gastrointestinal hemorrhage
- Bowel perforation
- Arthritis
- Nephrotic syndrome
- Renal failure (5%)
- Testicular torsion

Classification criteria for Henoch-SchonleinPurpura

Two of the following criteria must be present:

- Palpable purpura
- Age at onset ≤20 years
- Bowel angina (postprandial abdominal pain, bloody diarrhea)
- Biopsy demonstrating intramural granulocytes in small arterioles and/or venules

Differential diagnosis

- Idiopathic Thrombocytopenic Purpura (ITP)
- Meningococcemia
- Hemolytic uremic syndrome
- Systemic lupus erythematosis
- Child abuse

Management

- Generally treatment is supportive
- Adequate hydration

- Bland diet
- Pain control with paracetamol
- Avoidance of competitive activities
- Avoidance of maintaining the lower extremities in a dependent position may decrease local edema
- Corticosteroids
    - Dose is 1 mg/kg/day for 1–2 weeks.
    - Used in severe disease.
    - It may provide symptomatic relief for severe gastrointestinal or joint manifestations but does not help for skin or renal manifestations.
- Hydrostatic reduction or resection of the intussusceptions
- Chronic or recurrent HSP may respond to pulse doses of IV methyl-prednisolone (30 mg/kg/day, maximum 1 g/day, daily for 3 days followed by 1–2 times weekly and then tapered).
- Management of renal involvement includes azathioprine, cyclophosphamide, cyclosporine, and mycophenolate mofetil.

Prognosis

- HSP episodes are self-limiting and prognosis for recovery is generally good.
- Recurrences occasionally occur within 4–6 weeks in 15–60% of children.
- Long-term morbidity is related to chronic renal involvement in 1–2% children and 8% of those develop end stage renal disease.

KAWASAKI DISEASE

CASE

A 4-year-old boy presents with history of intermittent ***fever*** spiking to 104°F (40°C). On clinical examination, he has ***bilateral conjunctivitis***, dry cracked lips and ***strawberry tongue***. He also has a maculopapulartruncal***rash***, hand and foot ***edema***, and an enlarged but nonsuppurative right anterior ***cervical lymph node***. His fingers are ***peeling***. A grade II/VI systolic ejection ***murmur*** is heard. Angiography shows coronary arterial ***aneurysms***.

- It is an acute febrile disease first described in Japan.
- The illness occurs predominantly in young children. 80% of patients are younger than 5 years and can occur even before one year of age.

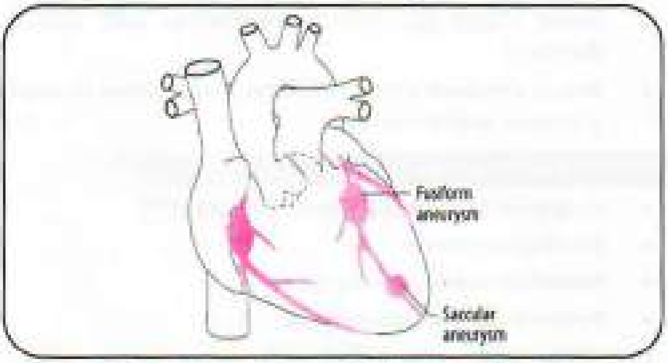


Figure 21.7 Types of aneurysms in Kawasaki disease

Pathogenesis

- Kawasaki disease causes a severe vasculitis of all blood vessels but predominantly affecting medium sized arteries like coronary arteries.
- In the 1st phase (1st week), there is necrotizing arteritis of endothelium of coronary artery and involves its wall forming saccular aneurysm.
- In the 2nd phase, there is subacute/chronic vasculitis which may last weeks to years and results in fusiform aneurysm.
- Finally, there is progressive stenosis and thrombus formation.

Diagnostic criteria

- Fever persisting at least 5 days.
- Presence of at least 4 principal features:
    1. Changes in extremities:
        - Acute: Erythema of palms, soles; edema of hands, feet
        - Subacute: Periungual peeling of fingers, toes in weeks 2 and 3
    2. Polymorphous exanthema
    3. Bilateral bulbar conjunctival injection without exudates
    4. Changes in lips and oral cavity: erythema, lip cracking, strawberry tongue, diffuse injection of oral and pharyngeal mucosa
    5. Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral
- Exclusion of other diseases with similar findings

Note

- Patients with fever at least 5 days and <4 principal criteria can be diagnosed with Kawasaki disease when coronary artery abnormalities are detected by echocardiography or angiography
- In the presence of ≥4 principal criteria, Kawasaki disease diagnosis can be made on day 4 of illness.

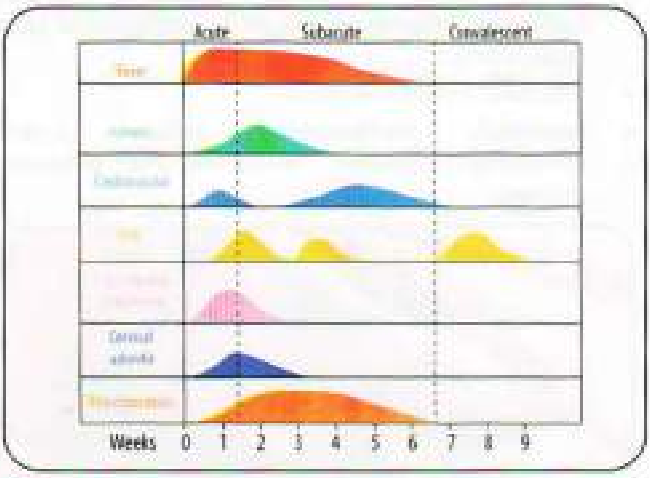


Figure 21.8 : Clinical findings of Kawasaki disease

Clinical findings: (1–2 weeks)

Acute febrile phase

- It is characterized by high fever (101°F) and not responding to antibiotics.

- Fever may persist for 1–2 weeks.
- There is exudative conjunctivitis, pharyngitis, generalized lymphadenopathy, discrete oral lesions and vesiculo-bullous skin rash.

Subacute phase: (4 weeks)

- It is associated with desquamation, thrombocytosis and development of coronary aneurysms.
- There is increased risk of sudden death during this phase.

Convalescent phase: (6–8 weeks)

Clinical signs of illness disappear and recovery starts.

Differential diagnosis

- Scarlet fever (patients older than typical patient with Kawasaki disease; no hand, foot, or conjunctival involvement)
- Group A streptococcal infection
- Stevens-Johnson syndrome (mouth sores, and cutaneous bullae and crusts are characteristic)
- Measles (rash occurs after fever peaks and begins in head/scalp). Some features of measles that distinguish it from Kawasaki disease include exudative conjunctivitis, Koplik spots, rash that begins on the face and behind the ears, leukopenia, and a normal ESR and/or CRP.
- Other viral infection (EBV, adenovirus).
- Juvenile idiopathic arthritis:
  - There is usually a longer duration of fever at presentation.
  - There is lymphadenopathy, hepatosplenomegaly, and an evanescent, salmon-colored rash.
- Drug reaction
- Toxic shock syndrome. Toxic shock syndrome is distinguished by the presence of hypotension, renal and hepatic dysfunction, elevated creatine phosphokinase level, and focal *Staphylococcus aureus* infection.
- Bacterial endocarditis
- Rheumatic fever

Diagnosis

- There is no diagnostic test for kawasaki disease. Diagnosis is mainly clinical.
- Hemoglobin–lowered (anemia)
- Leukocyte count:
  - Normal to elevated
  - Leukocytosis with neutrophilia and immature forms
- Platelets count is raised (thrombocytosis)
- ESR, CRP (C-reactive protein), and other acute phase reactants–raised
- Abnormal plasma lipids
- Antinuclear Antibodies (ANA) and Rheumatoid Factor (RF) are negative
- Hypoalbuminemia
- Hyponatremia
- Sterile pyuria
- Elevated serum transaminases
- Elevated serum gamma glutamyltranspeptidase
- Pleocytosis of cerebrospinal fluid
- Echocardiography (at diagnosis and again after 6 weeks, 6 months, or longer if abnormal). There may be pericardial effusion, coronary aneurysms, and aneurysms of peripheral arteries other than coronary.

Complications

Heart involvement

- Pericardial effusion
- Myocardial disease (poor contractility)
- Endocardial disease (valve regurgitation)
- Coronary disease:
  - Ectasia, dilatation
  - Small 3–5 mm aneurysms (resolve)
  - Medium 5–8 mm aneurysms (usually resolve)
  - Giant aneurysms >8 mm (ischemia later)
- Greatest risk if:
  - Male
  - <1 year
  - Fever >16 days
  - ESR >100
  - WBC count >30,000

Management

- Supportive care
- Treatment of Kawasaki disease is aimed at reducing inflammation and preventing the occurrence of coronary arterial aneurysms and arterial thrombosis

Acute stage

- Intravenous immunoglobulin 2 g/kg over 10–12 hours *with* aspirin 80–100 mg/kg/day divided every 6 hours orally for at least 48 hours.

Convalescent stage

- Aspirin 3–5 mg/kg once daily orally until 6–8 weeks after illness onset.
- Patients receiving long term aspirin therapy are candidates for annual influenza vaccination to reduce the risk of Reye syndrome. Varicella vaccination should be strongly considered.

Long-term therapy for those with coronary abnormalities

- Aspirin 3–5 mg/kg once daily orally ± clopidogrel 1 mg/kg/day (max 75 mg/day) (warfarin or low molecular weight heparin may be added for those patients at particularly high risk of thrombosis).

Acute coronary thrombosis

- Prompt fibrinolytic therapy with tissue plasminogen activator, streptokinase, or urokinase under supervision of a pediatric cardiologist.
- Acute thrombosis may occasionally occur in an aneurysmal or stenotic coronary artery. Thrombolytic therapy may be lifesaving in this circumstance.
- Aspirin: Antiplatelet dose: 3–5 mg/kg orally once a day every day.
- Unfractionated heparin: Load: 50 U/kg IV. Infusion: 20 U/kg/hour.
- Tissue plasminogen activator (tpA). Intravenous Bolus: 1.25 mg/kg; Infusion: 0.1–0.5 mg/kg per hour for 6 hours then reassess.
- Streptokinase or urokinase IV bolus 1000–4000 units/kg over 30 minutes; infusion 1000–1500 units/kg per hour.
- Urokinase: Bolus: 4400 U/kg over 10 minutes IV. Infusion: 4400 U/kg per hour.

Prognosis

- The prognosis for patients with coronary abnormalities depends on the severity of coronary disease.
- Recovery is complete and without apparent long-term effects for patients who get prompt treatment (risk of coronary aneurysm is less than 5%).
- Coronary aneurysms or widening occur in about 20% of cases.
- Recurrent acute illness occurs in only 1–3% of cases.
- Death is due to coronary vasculitis causing myocardial infarction or rupture of an aneurysm occurs in about 1% of cases.

CHAPTER 22

Human Genetics

INTRODUCTION

- Genetic abnormalities are gaining importance after control of infectious diseases. These are common cause of disease, death and prolonged handicap in infants and children.
- 1% of newborn infants will manifest monogenic disease (e.g. cystic fibrosis, sickle cell anemia).
- 0.5% will have chromosomal disorders (e.g. Down syndrome).
- 1–3% of children have diseases that are multi-factorial in pathogenesis (e.g. congenital heart disease, spina bifida).
- Approximately 40% of childhood deaths are due to genetic disorders and birth defects.
- Three types of genetic defects have been identified in humans:

Chromosomal abnormalities

Entire chromosomes or large segments of them are altered (duplicated, missing, translocated, etc.), e.g. trisomy 21 syndrome.

- Abnormalities of autosomes:
    - Down syndrome
    - Trisomies 18 and 13
- Abnormalities of sex chromosomes:
    - Turner syndrome
    - Klinefelter syndrome
- Other chromosomal abnormalities:
    - Fragile X syndrome

Single gene defects

Single genes are altered, e.g. cystic fibrosis, Tay–Sachs

- Autosomal dominant inheritance
- Autosomal recessive inheritance
- X-linked recessive inheritance
- X-linked dominant inheritance

Multi-factorial inheritance

Disorders due to a combination of genetic and environmental factors, e.g. cleft lip and palate.

Mitochondrial disorders

Disorders caused by alterations in the cytoplasmic mitochondrial DNA.

Mitochondria contain their own chromosomes, which are maternally derived.

Dysmorphology is the study of malformations and birth defects. Abnormal development may be due to a chromosomal abnormality, a single gene defect or a teratogen, or may be multi-factorial.

CHROMOSOMAL ABNORMALITIES

- According to some estimate about 7% of human conceptions have karyotyping abnormalities and 90% of them don't survive pregnancy. Among live born about half involve autosomes and half the sex chromosomes.
- Errors during cell division may result in chromosomal abnormalities, which are of two types:
    1. Abnormalities of chromosome number
    2. Abnormalities of chromosome structure

Abnormalities of chromosome numbers

- The commonest type of numerical abnormality is trisomy.
- ***Non-disjunction:*** It is the failure of autologous chromosomes to separate during cell division. Non-disjunction during first meiotic division results in either monosomic or trisomic individuals. While non-disjunction during second meiotic division gives rise to equal number of normal and abnormal individuals. If non-disjunction occurs in early stages of division of zygote then an individual carries one or possibly more cell lines known as mosaic. The older the mother, the greater the likelihood of non-disjunction and trisomy e.g. Down syndrome.
- The two common sex chromosomal abnormalities are Turner syndrome and Klinefelter syndrome.

Abnormalities of chromosome structure

- There are two types of structural abnormalities, either there is loss or gain of autosomal genetic material or there is structural rearrangement of existing genetic material.
- This has adverse effect on both mental and physical development.
- Deletions or loss of chromosomes material may result in a syndrome like Cri-du-chat.

Deletions

- In deletions genetic material of a chromosome is lost.

Translocation

- Translocation is detachment of a chromosome segment from its normal location and its attachment to another chromosome.

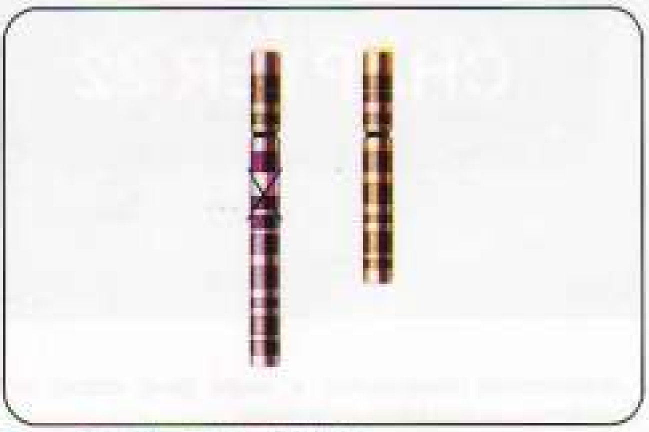


Figure 22.1: Illustration of deletion.

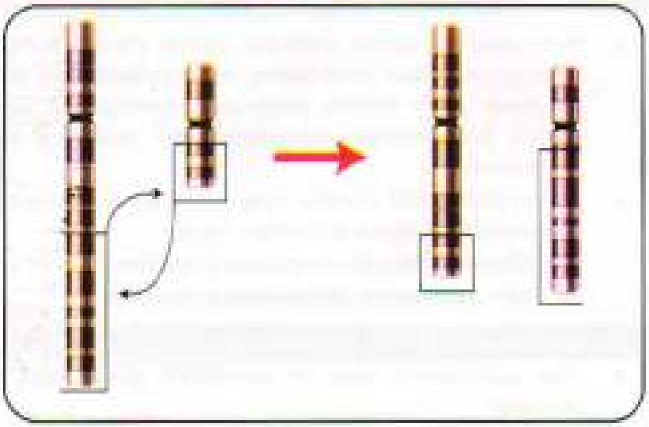


Figure 22.2: Illustration of translocation.

Mosaicism

- Mosaicism is the presence of two or more different chromosome constitutions in different cells of the same individual.
- For example, a patient may have some cells with 47 chromosomes and others with 46 chromosomes.

DOWN SYNDROME

(Trisomy 21)

CASE

A 36-year-old woman (***advanced maternal age***) delivers a baby girl. The infant has decreased tone, upslantingpalpebral fissures, ***epicanthal folds***, redundant nuchal skin, fifth finger ***clinodactyly***, a ***single transverse palmar crease***, and brachycephaly.

- Down syndrome is the most common autosomal trisomy compatible with life.
- The basic defect is trisomy, i.e. there are 47 chromosomes instead of 46.

Types of defects

- The characteristic finding and etiology of Down syndrome is trisomy 21, although some cases result from translocation or, more rarely, mosaicism.

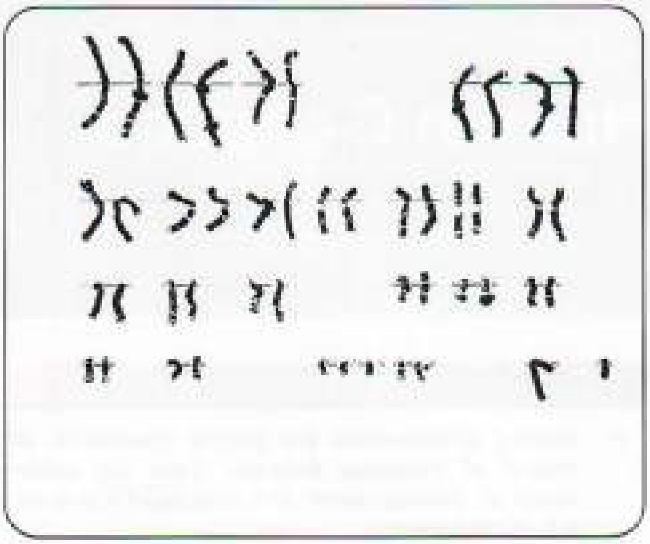


Figure 22.3: Karyotyping showing trisomy 21.

Trisomy 21

- 92% of children with Down syndrome have 47 chromosomes, with three 21 chromosomes.
- The additional number 21 chromosome is derived from the mother in 80% of cases.
- Trisomy 21 occurs in 1 in 700 live births.
- The recurrence risk for parents who have had a child with Down syndrome is 5–7%.
- Chromosomal *non-disjunction* during maternal meiosis is responsible for 80–92% of cases of trisomy 21.

Translocation

- 5% of children with Down syndrome have 46 chromosomes, with a translocation.

Mosaicism

- 3% of children with Down syndrome have chromosome mosaicism.
- Children with Mosaic Down syndrome may have a milder clinical presentation.

Clinical findings

- There is generalized hypotonia.
- Head circumference is small with a brachycephalic skull (flat occiput). Delayed closure of fontanels.
- Nasal bridge is flat with flat facies.

- Palpebral fissures slope upward. There may be marked epicanthic folds.
- Ears are small and low set.
- Tongue appears large and may protrude because the mouth is relatively small.
- Brushfield spots or speckled iris (whitish spots scattered round the periphery of the iris).
- Increased incidence of lens opacities is found.
- Eruption of teeth is frequently delayed with abnormalities in positioning.
- Hair may be fine and sparse.
- Velvety, loosely adhering mottled skin (cutis marmorata).
- Hands, feet and digits are short and broad.
- Clinodactyly (fifth finger is short and incurved).
- Lax joints
- Simian crease (a single transverse palmar crease) is seen in both hands in 50% of children with Down syndrome. A unilateral transverse palmar crease may be demonstrated in 2–5% of chromosomally normal infants.
- There is a wide space between 1st and 2nd toe and a deep plantar crease between the first and second toe.

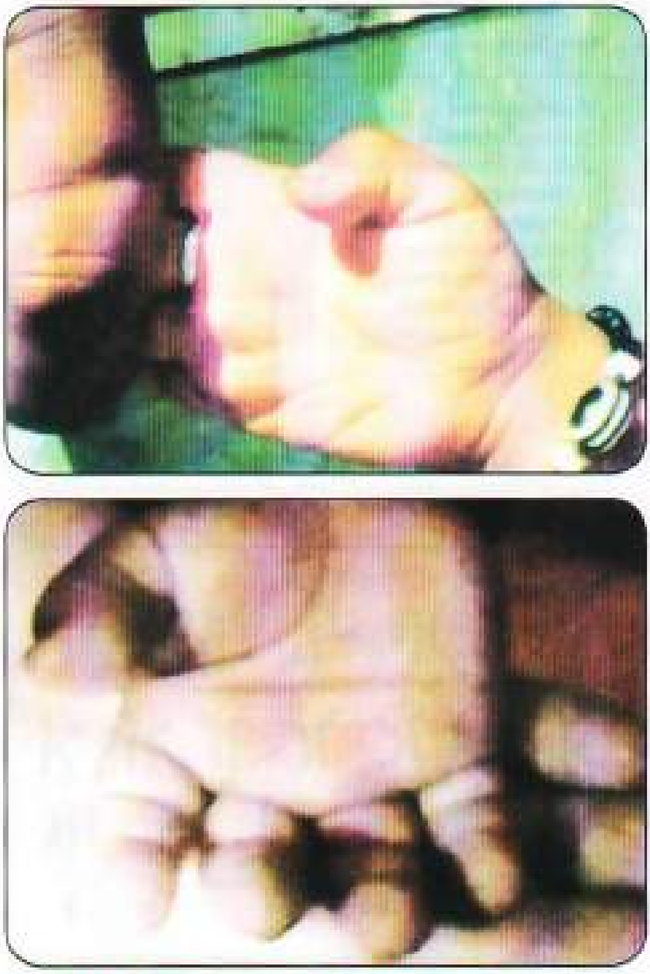


Figure 22.4 : Simian crease in Down syndrome.

- Dermatoglyphic features: an increase in ulnar loop, a single flexion crease on the fifth finger and a distal axial tri-radius.
- Congenital heart disease (occurs in 40–60% of infants with Down syndrome). Atrioventricular canal (endocardial cushion), TOF and ventricular septal defects are the commonest types of cardiac lesions.

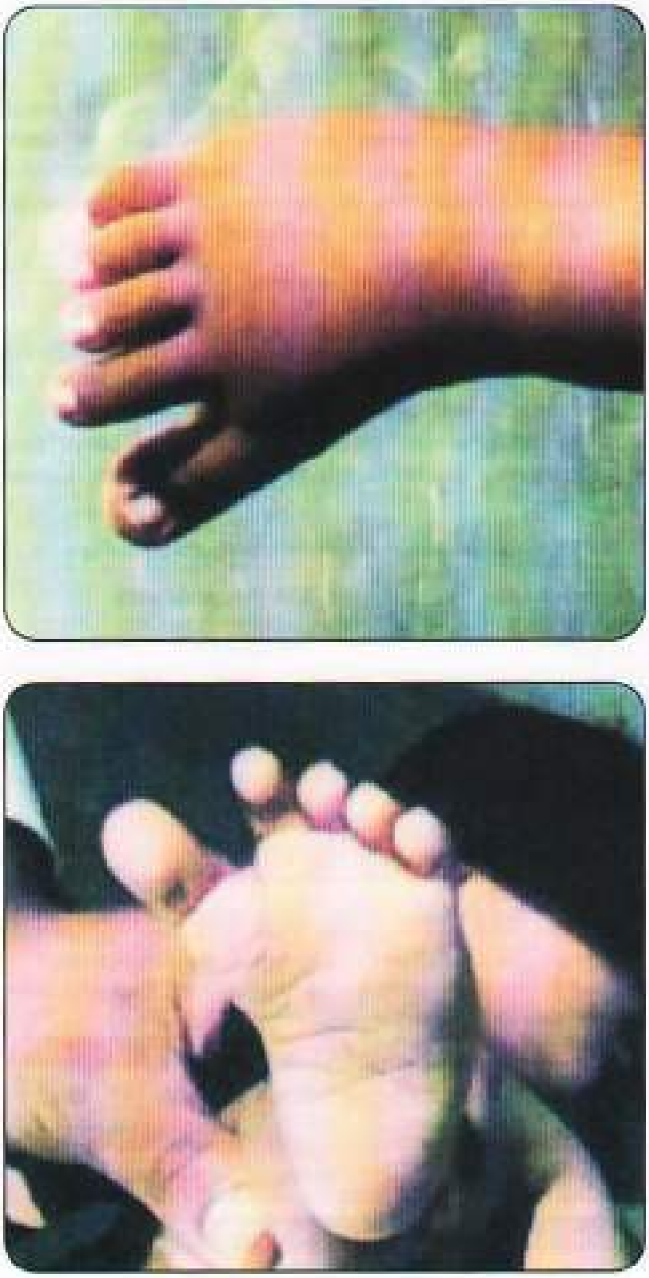


Figure 22.5: Foot in Down syndrome:
There is a wide space between 1st and 2nd toe.

- Structural abnormalities of bowel (tracheo-esophageal atresia, duodenal atresia, annular pancreas, Hirschsprung disease). One third of cases of congenital duodenal atresia occur in Down syndrome.

- The ultimate IQ ranges from 20–75 with a mean around 50.
- Children with Down syndrome are often affectionate and good humored.
- Development of secondary sexual characteristics is delayed.
- In males infertility is the rule. In females, although puberty is delayed they are usually fertile.
- Affected newborns may have prolonged physiologic jaundice, polycythemia, umbilical hernia, and a transient leukemoid reaction.
- Under two years of age, a megakarocytic acute myelogenousleukemia predominates, but in older children it is predominantly acute lymphoblastic leukemia. Leukemia is 20 times more common in Down syndrome than in unaffected children.
- Statistically, there is an increased risk for hypothyroidism.

Genetic counseling

- The risk of having a child affected with trisomy 21 varies with **maternal age**:
- The risk is also affected by the **parental karyotype**. Recurrence risk on karyotype status of parents is given below:

Table 22.1: Risk of Down syndrome with maternal age.

Maternal age	Risk (approximate)
All ages	1 in 650
30 years	1 in 1000
35 years	1 in 350
40 years	1in 100
45 years	1 in 50

Table 22.2: Recurrence risk of Down syndrome.

Patient	Father	Mother	Recurrence risk
Trisomy 21	Normal	Normal	1%
Translocation 21/21	Normal Carrier Normal	Carrier Normal Normal	100% 100% Slightly increased
Mosaic	Normal	Normal	1%

Diagnosis and screening

- Characteristic clinical picture
- Karyotyping: Chromosomal abnormalities are pathognomonic
- Triple screen during pregnancy:
  - Decreased ∝-fetoprotein
  - Decreased unconjugated estriol
  - Elevated chorionic gonadotropin (β-hCG) in blood samples taken around 12 weeks' gestation
- Quad screen during pregnancy: Estriol, β-hCG, inhibin and ∝-fetoprotein can detect up to 80% of Down syndrome compared to 70% in triple screen.
- Both tests (triple and quad screen) have 5% false-positive rate.
- Confirmation of Down syndrome depends on examination of the chromosomes in fetal cells obtained either by amniocentesis or by chorionic villus sampling.
- Another approach to screening is to use ultrasound scanning in the first trimester and to measure the amount of thickening over the back of the neck, i.e. increased nuchal translucency, is associated with greater risk of chromosomal abnormalities.

Management

- There is no known treatment for this disorder.
- Therapy is directed towards specific problems e.g. antibiotics for infection, digoxin or cardiac surgery for heart problems.
- Support for parents and family planning advice is important.

EDWARD SYNDROME

(Trisomy 18)

- Incidence 1:6000 births
- Low birth weight

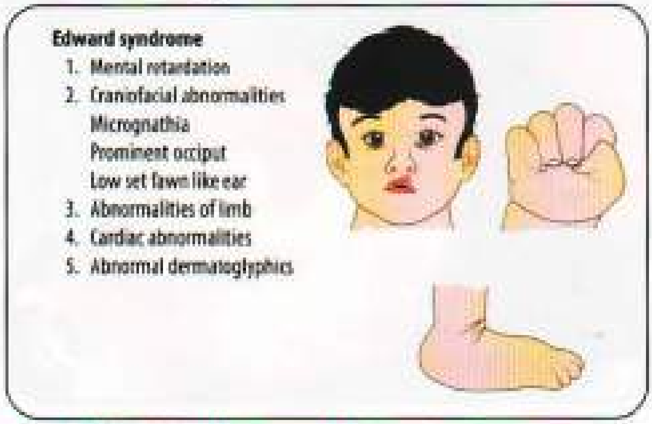


Figure 22.6: Clinical features of Edward syndrome.

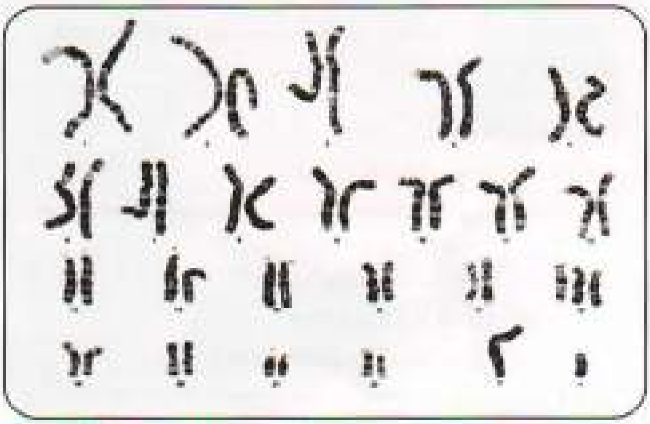


Figure 22.7 : Karyotyping showing trisomy 18.

- Closed fists with index finger overlapping the 3rd digit and the 5th overlapping the 4th
- Narrow hips with limited abduction
- Rocker-bottom feet
- Microcephaly
- Micrognathia
- Cardiac and renal malformations and mental retardation
- 95% of cases die in the 1st year

PATAU SYNDROME

(Trisomy 13)

- Incidence 1: 10,000 births
- Cleft lip (often midline)
- Flexed fingers with polydactyly
- Hemangiomas of the face,forehead, or neck
- Broad flat nose
- Low-set malformed ears
- Small abnormal skull, cerebral malformations
- Microphthalmia
- Cardiac malformation
- Hypoplastic or abnormal ribs
- Visceral and genetic anomalies
- About 91% die by 1 year. Survivors have significant neurodevelopmental delay.

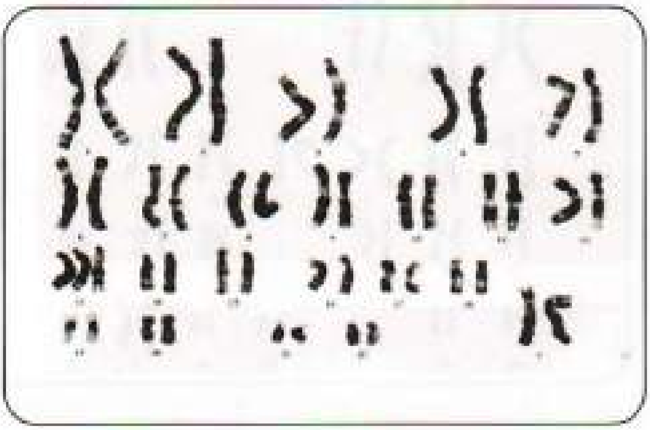


Figure 22.8 : Karyotyping showing trisomy 13.

TURNER SYNDROME

CASE

A 15-year-old girl presented with complaint of no menses (***primary amenorrhea***), wide carrying angle, webbed neck and ***short stature***. There is history of edema of the hands and feet in the newborn period. LH and FSH levels were greatly raised. Karyotype showed ***45XO***.

- Turner syndrome is a condition characterized by complete or partial monosomy of the X chromosome.
- Half of the patients with Turner syndrome have a 45X chromosome. The other half has mosaicism and varied structural abnormalities of the X or Y chromosome.
- Maternal age is not a factor for Turner syndrome in children with 45X.
- Turner syndrome occurs in approximately 1 in 2500 female live births.
- In 75% of patients, the lost sex chromosome is of paternal origin (whether an X or a Y).
- 45X is a chromosome abnormality most often associated with spontaneous abortion.

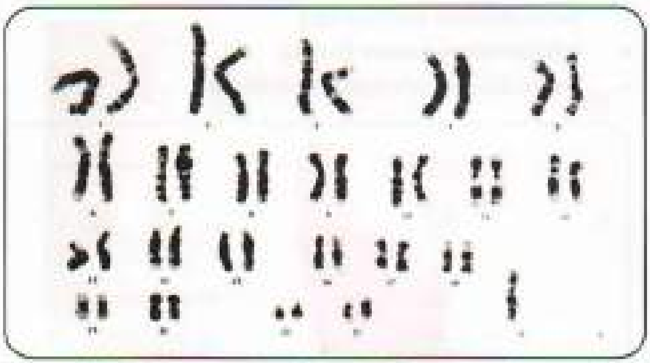


Figure 22.9 : Karyotyping showing Turner syndrome (only X chromosome, no Y chromosome).

Clinical findings

- Short stature
- Congenital lymphedema
- Horseshoe kidneys
- Patella dislocation
- Increased carrying angle of elbow (cubitus valgus)
- Congenital hip dislocation

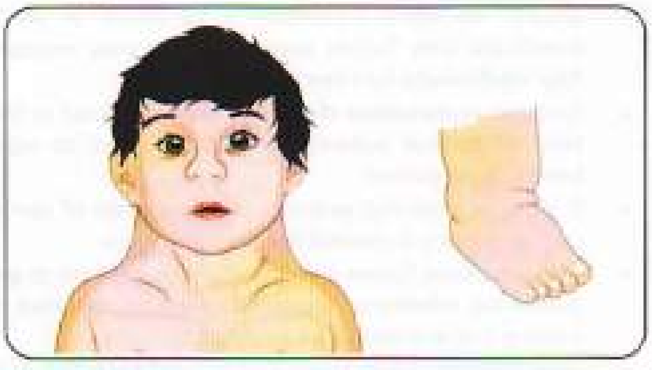


Figure 22.10: Turner syndrome.

- Scoliosis
- Widespread nipples
- Shield chest
- Redundant nuchal skin (in utero cystic hygroma)
- Low posterior hairline
- Coarctation of aorta
- Bicuspid aortic valve
- Cardiac conduction abnormalities
- Hypoplastic left-heart syndrome and other left-heart abnormalities

- Gonadal dysgenesis (infertility, primary amenorrhea)
- Gonadoblastoma (increased risk if Y chromosome material is present)
- Learning disabilities
- Developmental delay (in 10%)
- Hypothyroidism (acquired in 15–30%)
- Type 2 diabetes mellitus (insulin resistance)
- Strabismus
- Cataracts
- Red-green color blindness (as in males)
- Recurrent otitis media
- Sensorineural hearing loss
- Inflammatory bowel disease
- Celiac disease (increased incidence)

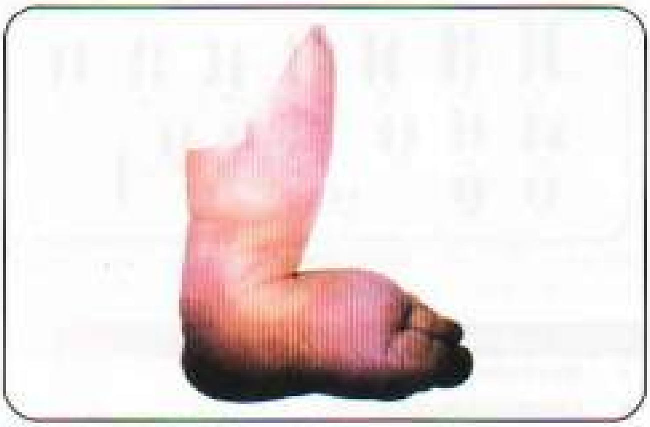


Figure 22.11: Pedal edema in Turner syndrome.

Management

- There is no cure for Turner syndrome, but many of the associated symptoms can be treated.
- Growth hormone treatment is beneficial in some individuals with Turner syndrome. This may increase final adult height by a few inches.
- Estrogen replacement therapy is usually started at the time of normal puberty, around 12 years to start breast development.
- If there is a cardiac problem or coarctation of aorta, cardiac surgery is needed at appropriate age.
- Girls who have Turner syndrome are more likely to get middle ear infections. Repeated infections may lead to hearing loss and should be evaluated.
- Hypertension is common in Turner syndrome. This may be due to coarctation of aorta or a kidney abnormality. This is treated by treating the cause and anti-hypertensive therapy.
- Almost all women are infertile. Women with Turner syndrome who wish to become pregnant may consider using a donor ovum.
- Having appropriate medical treatment and support, a girl with Turner syndrome may lead a normal, healthy and happy life.

KLINEFELTER SYNDROME

CASE

A ***tall*** 15-year-old boy seems to be much more ***immature*** for his age. He is delayed in his speech development and school work (***developmental delay***). On physical examination, he has ***long limbs*** and breast development (***gynecomastia***). His testes are small for age, and his phallus seems undersized (***hypogonadism***). His ***karyotyping*** shows 47XXY.

- Affects 1 in 1000 newborn boys and is caused by an extra X chromosome.
- In 80% of boys with Klinefelter syndrome, there is a 47 XXY karyotype. In 20% there is mosaicism.
- Boys are taller than average, with an arm span greater than their height.
- Incompletely masculinized, a female body habitus, female escutcheon, decreased body hair.
- Gynecomastia
- Testes remain small with greatly diminished spermatozoa production, infertility, seminiferous tubules dysgenesis.
- Mild mental retardation, behavioral problems

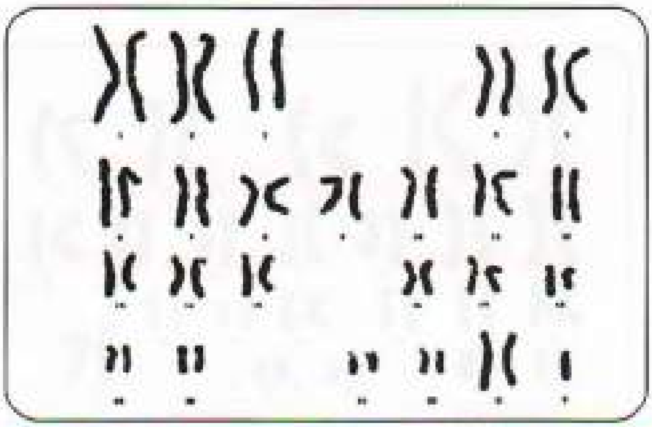


Figure 22.12: Karyotyping showing Klinefelter syndrome (two X chromosomes, one Y chromosome).

SINGLE GENE DEFECTS

- A gene is the unit of inheritance that determines the genetic makeup of an individual. Genes occur in pairs at a single locus or site on specific chromosome. These paired genes, called alleles, determine the genotype of an individual at that locus.
- If a single copy of the gene has a detectable effect when present, the condition is said to be dominant.
- If a disease manifest itself in the presence of two functionally identical mutant genes (i.e. it would be in-apparent if only one mutant gene is present), then the condition is termed as recessive.

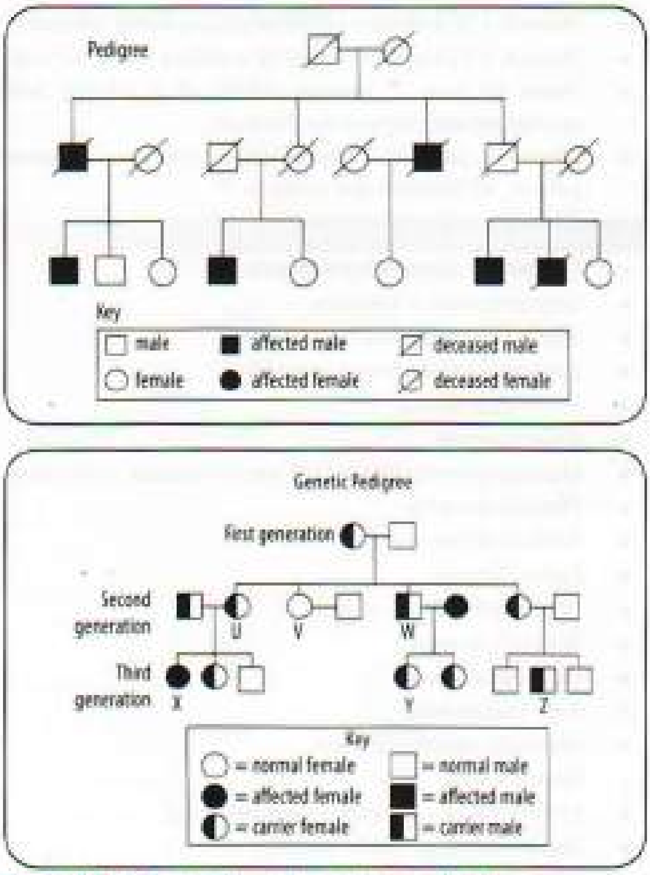

Pedigree
Key
male
affected male
deceased male
female
affected female
deceased female
Genetic Pedigree
First generation
Second generation
Third generation
U
V
W
X
Y
Z
Key
= normal female
= normal male
= affected female
= affected male
= carrier female
= carrier male

Figure 22.13: Symbols used in pedigree charts.

- If an individual has two identical alleles, the person is said to be homozygous for the gene.
- If an individual has two different alleles, the person is heterozygous for the gene in question.
- The effects of recessive conditions are observed only in homozygous person, whereas the effects of dominant conditions are observed in the heterozygous individuals.
- Except for genes on the X and Y-chromosomes in males, all genes are duplicated in a normal diploid individual.

AUTOSOMAL DOMINANT INHERITANCE

Characteristics

- Males and females are equally affected.
- There are 1 in 2 chances (50%) of an offspring being affected and 50% will be normal.
- Heterozygous are severely affected e.g. early lethality in achondroplasia and familial hypercholesterolemia.
- Dominant inheritance is typically said to be ***'vertical'***, i.e. the condition passes from one generation to the next in a vertical fashion.
- The disease is seen in all generations.
- There is no carrier state.
- Unaffected members of the family are normal and do not transmit the disease.
- In some cases, the family history seems to be completely negative, and the affected individual appears to be first abnormal case. This spontaneous appearance may be caused by a point mutation or a change in the structure of a specific gene.
- Dominant conditions are not caused by enzyme defects. Dominant traits are more often related to structural abnormalities of protein, as for example Marfan syndrome.

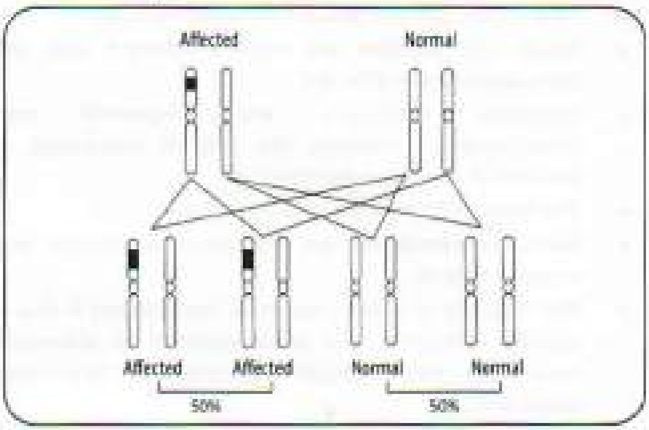

Affected
Normal
Affected
Affected
Normal
Normal
50%
50%

Figure 22.14: Autosomal dominant inheritance.

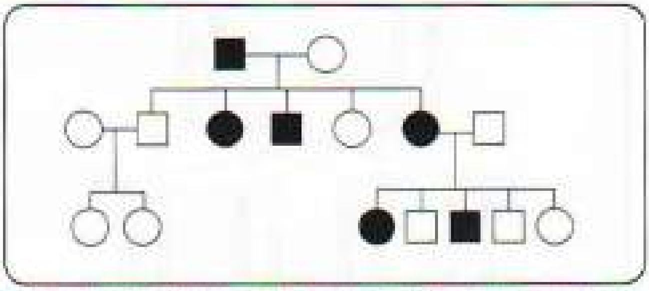


Figure 22.15: Autosomal dominant inheritance pedigree. The disease is seen in all generations. There is no carrier state. (Vertical transmission)

Autosomal dominant disorders

- Achondroplasia
- Congenital spherocytosis
- Epidermolysisbullosa simplex
- Marfan syndrome
- Neurofibromatosis
- Tuberous sclerosis
- Osteogenesis imperfect
- Polycystic kidney disease
- von-Willebrand disease
- Retinoblastoma (bilateral)
- Myotonic dystrophy
- Huntington's chorea
- Alagille syndrome
- Ehlers–Danlos syndrome (most)
- Facioscapulohumeral muscular dystrophy
- Familial adenomatous polyposis
- Familial hypercholesterolemia

- Gilbert syndrome
- Noonan syndrome
- Porphyrias (except congenital erythropoietic which is autosomal recessive)

(Note–conditions pre-fixed 'hereditary' or 'familial' are usually autosomal dominant)

AUTOSOMAL RECESSIVE INHERITANCE

Characteristics

- Parents are carriers and are clinically normal.
- Males and females are equally affected and only homozygotes are affected.
- Recessive conditions are frequently rare. Consanguinity increases the risk of expressing an autosomal recessive disorder.
- The family history is usually negative.
- Recessive conditions are frequently associated with enzyme defects.
- The majority of inborn errors of metabolism is due to specific deficiency and is transmitted as autosomal recessive trait except porphyrias (autosomal dominant).

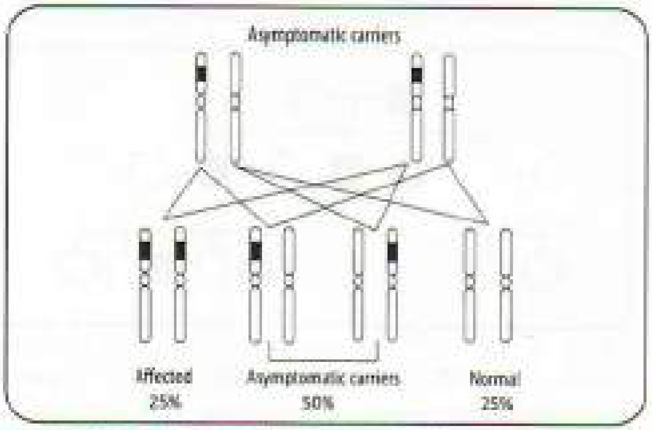


Figure 22.16: Autosomal recessive inheritance.

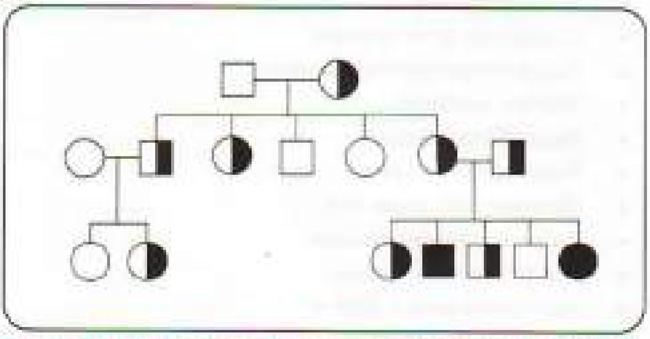


Figure 22.17: Autosomal recessive inheritance pedigree. Recessive conditions are clinically manifest only when an individual has two copies of the mutant allele. When just one copy of the mutant allele is present, an individual is a carrier of the mutation, but does not develop the condition. Females and males are affected equally by traits transmitted by autosomal recessive inheritance. Horizontal transmission)

- There is 1 in 4 chance (25%) of sibling being affected.
- There is 1 in 4 chance (25%) of a sibling being normal.
- There is 1 in 2 chance (50%) of a sibling being asymptomatic carriers for the trait.
- When a patient (homozygous) marries a normal person, all children are carriers.

Autosomal recessive disorders

- Congenital adrenal hyperplasia
- Oculocutaneous albinism
- Ataxia telangiectasia
- Epidermolysisbullosadystrophica
- Friedrich's ataxia
- Galactosemia
- Mucopolysaccharidoses (all except Hunter syndrome)
- Phenylketonuria
- Sickle cell anemia
- Cystic fibrosis
- Werdnig-Hoffman disease
- Wilson's disease
- Gaucher disease
- Beta thalassemia
- Glycogen storage disease
- Alkaptonuria
- Crigler–Najjar syndrome (severe form)
- Dubin–Johnson syndrome
- Fanconianemia
- Glucose-6-phosphatase deficiency (von Gierke diseased)
- Homocystinuria
- Hemochromatosis
- Spinal muscular atrophies
- Xerodermapigmentosa

X-LINKED RECESSIVE INHERITANCE

- There is practically no genetic material on Y chromosome except those, which determine sexual development, and all genetic material is carried on X chromosome. So sex linked diseases are called X-linked.
- In X-linked recessive trait, the mutant gene is present on the X chromosome and is carried by females to affect males.
- The affected males are homozygous (with mutant gene on their single X chromosome) while carrier females are heterozygous and perfectly healthy (defect is balanced by second normal X chromosome).
- The affected male can transmit the disorder through their daughters unless the disorder is so severe that the affected males don't survive to have children, e.g. Duchenne muscular dystrophy.

Characteristics

- Males are affected.
- Heterozygous females are either normal or have mild manifestations.

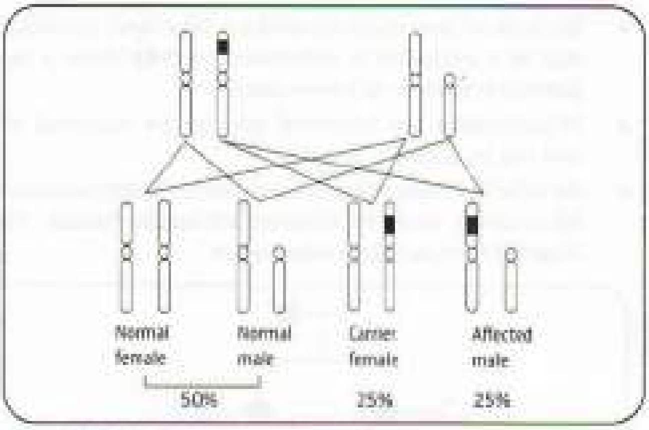


Figure 22.18: X-linked recessive inheritance.

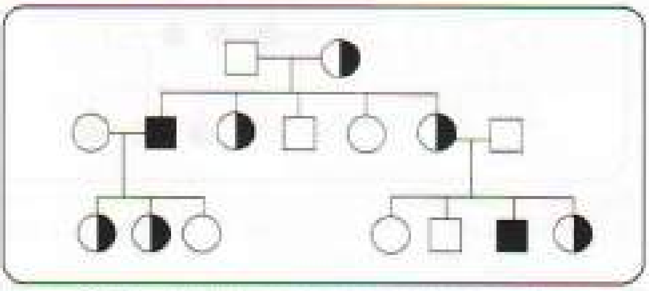


Figure 22.19: X-linked recessive inheritance pedigree. X-linked recessive traits are not clinically manifest when there is a normal copy of the gene. All X-linked recessive traits are fully evident in males because they only have one copy of the X chromosome, thus do not have a normal copy of the gene to compensate for the mutant copy. For that same reason, women are rarely affected by X-linked recessive diseases; however they are affected when they have two copies of the mutant allele. Because the gene is on the X chromosome there is no father to son transmission, but there is father to daughter and mother to daughter and son transmission. If a man is affected with an X-linked recessive condition, all his daughters will inherit one copy of the mutant allele from him.

- Inheritance is *'diagonal'* through the maternal side of family.
- There is 1 in 2 chance (50%) for transmitting the gene to the offspring.
- There is 1 in 2 chance (50%) of the daughters being a carrier and (50%) being normal.
- There is 1 in 2 chance (50%) of mother being a carrier, then a son being affected and 50% being normal.
- All of the daughters of an affected male are carriers, and none of his sons are affected (i.e. male to male transmission cannot occur).
- The mutation rate is high in some X-linked disorders, particularly when the affected male is infertile.

X-Linked recessive disorders

- Color blindness
- Duchenne muscular dystrophy
- Becker muscular dystrophy
- Hemophilia A and B
- Nephrogenic diabetes insipidus
- G6PD deficiency
- Hunter's syndrome
- Lesch-Nyhan syndrome
- Fabry disease
- Fragile X syndrome
- Testicular feminization syndrome
- Wiskott–Aldrich syndrome

X-LINKED DOMINANT INHERITANCE

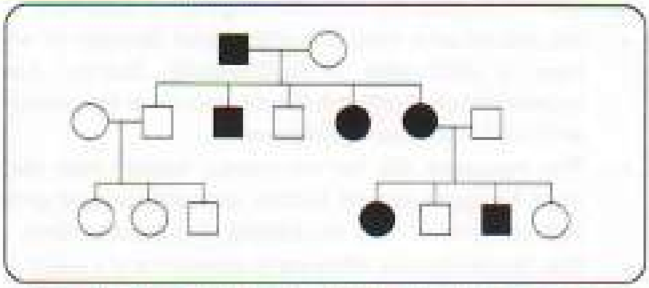


Figure 22.20: X-linked dominant inheritance pedigree. Because the gene is located on the X chromosome, there is no transmission from father to son, but there can be transmission from father to daughter (all daughters of an affected male will be affected since the father has only one X chromosome to transmit). Children of an affected woman have a 50% chance of inheriting the X chromosome with the mutant allele. X-linked dominant disorders are clinically manifest when only one copy of the mutant allele is present.

Characteristics

- It can manifest in heterozygous female and in homozygous male.
- The heterozygous female is symptomatic, and the disease is twice as common in females because they have two X chromosomes that can be affected.
- The risk for the offspring of heterozygous females is 50% regardless of sex.
- All of the daughters of the affected male will have the disorder and all the sons will be normal.
- Although a homozygous female is possible, she would be severely involved. All of her children would also be affected, but more mildly.

X-Linked dominant disorders

- Incontinentiapigmenti
- Pseudohypoparathyroidism
- Vitamin D resistant rickets
- Chondrodysplasiapunctata
- Goltz syndrome
- Rett syndrome

POLYGENIC (MULTI-FACTORIAL) INHERITANCE

- Multifactorial disorders are conditions that are believed to be caused by a combination of genetic liability and environmental (non-genetic) factors.
- Many common birth defects and many common disorders of midlife are due to multifactorial inheritance.
- The general population incidence of most multifactorial disorders is 1.0–1.5 per 1000 for each condition.
- The risk is generally less than single gene disorders.
- Individuals who have a multifactorial disorder or who have a child with a multifactorial disorder have approximately 2–5% risk for recurrence of the disorder with each subsequent pregnancy.
- The increased risk for recurrence implies that there must be some genetic factors, probably several genes that play a role in the occurrence of these disorders.
- Risk to siblings and offspring is approximately equal.
- Unlike single gene disorders the recurrence risk for multifactorial disorders increases with an increasing number of affected relatives and increasing severity of the disorder.
- There is a difference in male (M) to female (F) ratio of several multifactorial disorders e.g. congenital hip dislocation (F>M) and pyloric stenosis (M>F).
- The recurrence risk is greater when the affected individual is more severely affected. The recurrence risk is greater when a child has bilateral cleft lip and palate compared to isolated cleft lip.

Multi-factorial disorders

- Cleft lip and/or cleft palate
- Pyloric stenosis
- Asthma
- Diabetes mellitus
- Neural tube defects (spina bifida)
- Congenital heart disorders
- Congenital dislocation of hip, clubfoot
- Idiopathic mental retardation
- Idiopathic epilepsy
- Hirschsprung's disease

MITOCHONDRIAL INHERITANCE

- The transmission of the mitochondrial genome from mother to child.
- Mitochondria contain their own set of genes which are chiefly involved in metabolic processes. This is in addition to the genes in the cell's nucleus.
- Alterations in the mitochondrial DNA cause several well recognized disorders, often associated with neuromuscular features.
- Because of how mitochondria are inherited, conditions due to a *mutation in mitochondrial DNA* show a very particular pattern of inheritance.
- Mitochondria are inherited only in the maternal ova and not in sperm.
- An affected male does not pass on his mitochondria to his children, so all his children will be unaffected. *This is called mitochondrial inheritance.*

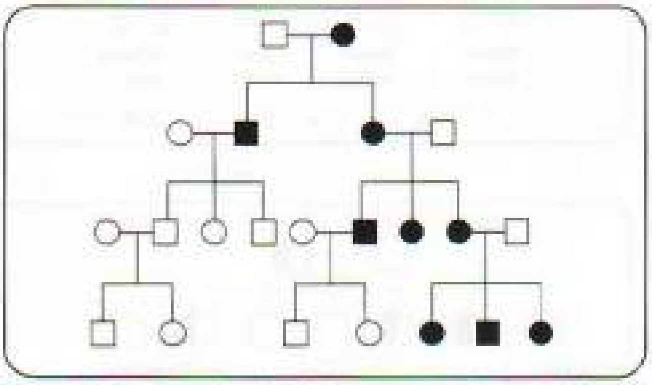


Figure 22.21: Mitochondrial inheritance pedigree. Affected father produces no affected offspring, while the offspring of affected mother are all affected.

Disorders due to mitochondrial inheritance

- Mitochondrial myopathy
- Diabetes mellitus and Deafness (DAD) combination
- Leber's hereditary optic neuropathy
- Leigh syndrome
- Myoclonic Epilepsy with Ragged Red Fibers (MERRF)
- Mitochondrial myopathy, Encephalomyopathy, Lactic acidosis, Stroke-like symptoms (MELAS)

GENETIC COUNSELING

- It is the process by which an individual is informed about the possibility of developing a disorder or transmitting it to his offspring and the chances of his offspring having similar disorder.
- Pediatrician or general practitioner who offers genetic counseling is called counselor. He should advise the parents about future child bearing.
- Important steps in genetic counseling are history and pedigree construction, examination, diagnosis, counseling and follow up.

Basic protocol for genetic counseling

- Take a careful family history and construct a pedigree.
- Document the prenatal, pregnancy, and delivery history.
- Review the available information concerning the disorder.
- Careful physical examination of the affected individual and of apparently unaffected individuals.
- Establish an accurate diagnosis by the diagnostic tests available.

- Mode of inheritance (e.g. autosomal recessive or dominant, X-linked or chromosomal abnormalities or mutation) should be established and explained to the parents.
- Possible help should be offered regarding the management of present disease.
- Detection of sex and diagnosis of disease during pregnancy should be established by amniocentesis. So parents can decide to have or not to have a baby.
- Outcome should be explained in statistical way for each pregnancy.
- Good knowledge regarding the disease should be provided to parents. Etiology, prognosis and management of the disorder in question should be discussed.
- Provide new information to the family as it becomes available.
- The timing of genetic counseling is also important. There is a fine line between counseling that is too early (because the family, still concerned about the welfare of the affected individual, is emotionally unprepared) and counseling that is too late (because another at risk fetus has already been conceived).

PRE-NATAL DIAGNOSIS

- Prenatal diagnosis introduces options for management that ranges from interruption of abnormal pregnancies to preparation for specialized perinatal care.

Methods of prenatal diagnosis

- Maternal blood screening
- Fetal cells in maternal blood (research only)
- Fetal ultrasound
- Fetal X-ray (for skeletal defects)
- Fetal MRI
- Amniocentesis
- Chorionic villus sampling
- Fetal skin biopsy (Albinism, Epidermolysisbullosa, Xerodermapigmentosum)

Maternal blood

- Elevated alpha fetoprotein:
    - Twins
    - Intestinal obstruction
    - Congenital nephrosis
    - Neural tube defects
    - Omphalocele
- Decreased alpha fetoprotein:
    - Trisomy 21
- Elevated chorionic gonadotropin:
    - Trisomy 21
    - Triploidy
- Decreased chorionic gonadotropin:
    - Trisomy 13
    - Trisomy 18
- Decreased unconjugated estriol:
    - Trisomy 21

Ultrasonography

- Trans-abdominal real-time ultra-sonography can visualize all major fetal organs as early as 16–18 weeks of gestation.
- Important defects detected by USG are:
    - Hydropsfetalis
    - Hydronephrosis
    - Neural tube defects
    - Intestinal obstruction
    - Congenital heart defects
    - Diaphragmatic hernia
    - Gastroschisis
    - Omphalocele
    - Limb reduction anomalies
    - Assessment of growth

Cordocentesis

- Fetal blood can be directly sampled in late gestation through ultrasound-guided Percutaneous Umbilical Blood Sampling (PUBS). Important diseases detected by PUBS are:
    - Fetalanemia
    - Thrombocytopenia
    - Thalassemia
    - Fetal oxygenation and acid-base disorders
    - Cells for DNA
    - Fetalhypoalbuminemia

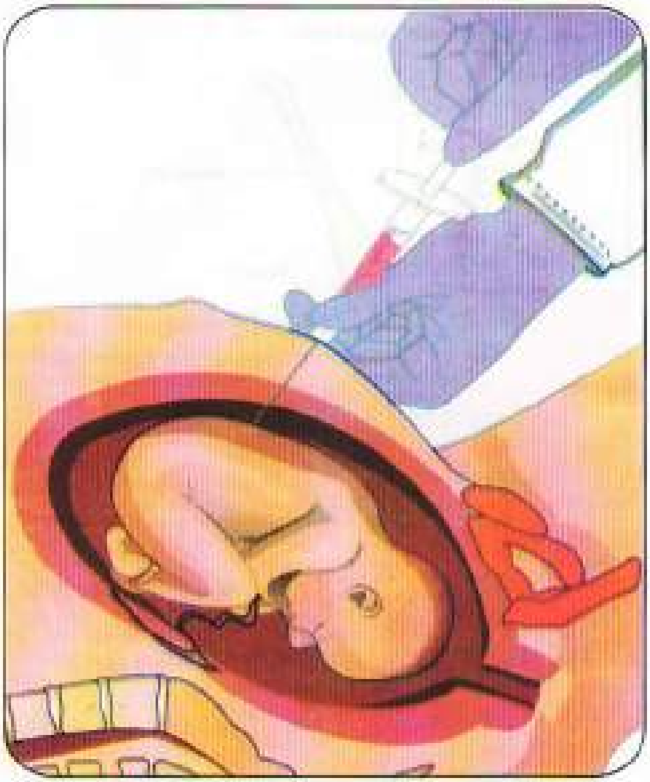


Figure 22.22: Amniocentesis.

Amniocentesis

- Fluid surrounding the fetus is sampled, and cells are cultured for cytogenetic, molecular, or metabolic analysis. Alpha feto-protein can also be measured.
- Amniocentesis can be performed as early as 10–14 weeks of gestation.
- This is a safe procedure with a complication rate (primarily for miscarriage) of less than 1% in experienced hands.

Chorionic villus sampling

- CVS (placental) is performed late in the first trimester (10–12 weeks).
- Tissue obtained by CVS provides more DNA for molecular analysis and contains dividing cells (cytotrophoblasts) that can be rapidly karyotyped.
- DNA analysis is done to detect thalassemia, hemophilia A, phenylketonuria, congenital adrenal hyperplasia, α_1-antitrypsin deficiency, etc.
- Karyotyping is done for trisomy 13, 18, 21; chromosomal deletions, Turner syndrome, Klinefelter syndrome, etc. However, direct cytogenetic preparations may be of poor quality. In addition, chromosomal abnormalities detected by this technique may be confined to the placenta (confined placental mosaicism).

Indications for amniocentesis and chorionic villus sampling

- Maternal age over 35 years

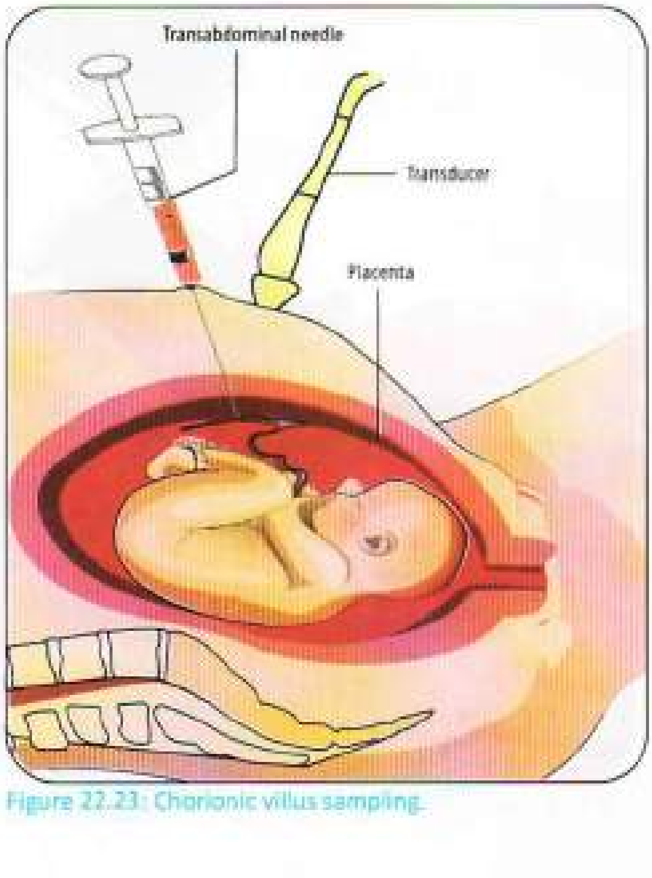


Figure 22.23: Chorionic villus sampling.

- Previous child with a chromosome abnormality
- Either parent a translocation carrier; the risk for a fetus with an unbalanced chromosome abnormality depends on the type of translocation.
- A history of any genetic disorder diagnosable by biochemical technique or by DNA analysis.
- A request by the parents for fetal sex determination because of a history of an X-linked disorder that is not otherwise diagnosed. Maternal blood testing (e.g. triple screen) indicating increased risks for chromosomal abnormalities.
- As part of the work up of fetal anomalies found by ultrasonography.

OTHER PEDIATRICS SYNDROMES

FRAGILE X SYNDROME

CASE

A 7-year-old boy is brought for his ***hyperactive behavior***. He also has ***speech and hearing problems***. He has large head, large ears and prominent forehead. He also has ***large testicles***.

- The most common inherited cause of mental retardation is fragile X syndrome.
- Fragile site is located on distal long arm of chromosome X.

Clinical findings

- Mental retardation, macro-orchidism, seizures
- Affects 1:1000 males.
- Female carriers may also be affected, often mildly.
- Affected males have developmental delay, hyperactivity, autism, oblong facies, large ears, large testicles, hyperextensible joints, mitral valve prolapse.
- 50% of affected females have normal IQ. 50% have mild to moderate learning disabilities and behavioral problems.
- Aggressive behavior stimulated by anxiety, impulsivity, hyperarousal, and mood instability affects 40% of males with fragile X. It may worsen during puberty.

Diagnosis

- DNA analysis can identify the amplified area in affected individuals and carriers.
- Prenatal diagnosis by chorionic villus sampling or amniocentesis is possible.
- This diagnosis is considered in male children with behavioral problems, learning disabilities or autism, and mild facial dysmorphism.

Management

- Language and motor therapy
- Therapy for behavioral problems

- Psychopharmacology can also be useful to treat ADHD, aggression, anxiety, or severe mood instability.
- Stimulant medications such as methylphenidate are usually beneficial.
- Anticonvulsants such as carbamazepine, valproic acid, and gabapentin can be used to treat seizures, which occur in about 20% of children with fragile X syndrome.
- An important part of treatment is genetic counseling. There is a high risk that other family members are carriers or may be affected by the syndrome.

LAURENCE-MOON-BIEDLE SYNDROME

CASE

A 10-year-old boy presents with limp. He is obese since infancy. His developmental milestones are delayed. On examination, he is very obese (49 kg). External genitalia show hypogonadism. Both feet show polydyctyly. Right hand shows syndactyly. Ophthalmic examination shows retinitis pigmentosa.

Clinical findings

- Autosomal recessive inheritance
- Short stature
- Mental retardation
- Obesity does not present until after infancy but most are obese by 4 years
- Retinitis pigmentosa/strabismus
- Polydactyly/clinodactyly
- Hypogonadism and pubertal failure due to deficiency in gonadotrophins
- Renal abnormalities
- Diabetes mellitus

PRADER-WILLI SYNDROME

CASE

A 5-year-old boy presents with the complaint of obstructive sleep apnea. He is obese. He has almond-shaped eyes, thin upper lip, and down turned corners of the mouth. The neurological exam is notable for diffuse hypotonia.

- Paternal chromosome is responsible. Inheritance is due to absence of paternal contribution to chromosome 15 (15q11–13), as a result of either deletion or maternal uniparentaldisomy.
- There is negligible recurrence risk.
- Reduced fetal movements and breech presentation are common.
- Presents in neonatal period with hypotonia, dysmorphism and feeding difficulties.
- Failure to thrive in infancy is common before developing marked hyperphagia and obesity in childhood.

Clinical findings

- Initially poor growth. Obesity (onset from 6 months to 6 years)
- Developmentally delayed (low IQ)
- Hypogonadism
- Short stubby hands
- Polydactyly
- Eyes (retinitis pigmentosa)
- Neonatal hypotonia
- Coarse facies
- Umbilical hernia
- Infants have profound hypotonia needing tube feedings, undescended testicles, and micropenis in males.
- Older children have characteristic facies (almond-shaped eyes, strabismus) short stature, obesity, hyperphagia, hypogenitalism, small hands and feet.
- Problems secondary to obesity are diabetes mellitus, orthopedic problems, sleep apnea, and corpulmonale.
- These children may develop Pickwickian syndrome of obesity, apnea, and right-sided heart failure.

Differential diagnosis

- Exogenous obesity from overfeeding.
- Congenital hypothyroidism (hypotonia, macroglossia, obesity, and growth failure).
- Bardet-Beidal syndrome.
- Down syndrome.
- In neonatal period other causes of the floppy infant should be ruled out.

Complications

- Pickwickian syndrome
- Diabetes mellitus
- Hypertension
- Osteoarthritis

Management

- Main goal of therapy is the prevention of obesity.
- Growth hormone increases muscle mass and promotes linear growth.
- Testosterone is effective for micropenis in males.
- Hormone replacement at adolescence may promote secondary sexual characteristics.

BECKWITH-WIEDEMANN SYNDROME

Case

A 36-week-gestation infant was delivered ***weighing 3.9 kg***. He had an ***omphalocele*** and a large tongue. There was no other abnormality observed. On laboratory investigations, there was ***hypoglycemia***.

- This syndrome is characterized by:
    - Neonatal macrosomia (enlarged body size)
    - Macroglossia (enlarged tongue)
    - Omphalocele
- Other associated findings include:
    - Mild facial dysmorphism (hypertelorism, horizontal ear lobe creases)
    - Infantile hypoglycemia due to transient hyperinsulinemia
    - Multiple congenital anomalies (cleft palate and genitourinary anomalies common)
    - Organomegaly (enlarged kidneys, liver or spleen)
    - Increased risk for certain malignancies, especially Wilmstumor
- Sporadic and autosomal dominant inheritance is present.
- Unrecognized neonatal hypoglycemia may result in mental retardation.

Associations

- Neonatal hypoglycemia due to islet cell hyperplasia.
- Accelerated growth and bone maturation
- Diaphragmatic eventration
- Hemihypertrophy is seen in 10% of those developing Wilmstumor.

Management

- Control of hypoglycemia (which may be refractory).
- Macroglossia may need partial glossectomy
- Obtain abdominal ultrasounds and serum AFP (alpha feto-protein) every 6 months through 6 years of age to look for Wilmstumor or hepatoblastoma.

NOONAN SYNDROME

- Incidence is 1:2500 births
- Sex distribution is equal
- Autosomal dominant gene defect

Clinical findings

- Short stature, delayed puberty, hypertelorism and other eye problems, low-set ears, mild mental retardation (25%), micropenis and cryptorchidism in males, delayed puberty pectusexcavatum with low-set wide-spaced nipples, webbed neck, and coagulation defects.
- 50–80% have pulmonary valve stenosis or hypertrophic cardiomyopathy.
- There is increased risk of myeloproliferative disorders and juvenile myelomonocyticleukemia.

Diagnosis

- This is usually a clinical diagnosis in newborns.
- Molecular genetic testing by sequence analysis is available.
- Intrauterine ultrasound often detects edema.
- Exclude Turner syndrome mosaic in females, which have a similar phenotype.

Differential diagnosis

- Turner syndrome (very similar phenotype)
- LEOPARD syndrome (lentigines, cardiac arrhythmia, pulmonary stenosis, hypertelorism, growth failure, genital abnormalities, and deafness).
- Costello syndrome (similar features but gene defect not identified)
- Cardio-facial-cutaneous syndrome (heart, skin, and growth problems)

Management

- Growth hormone therapy is helpful, but some patients have growth hormone resistance.
- Monitoring for bleeding disorders, myeloproliferative disorders.
- Hormone therapy may be required at puberty.
- Cardiac defects may require specialty care. Hypertrophic cardiomyopathy can develop at any time.

WILLIAMS SYNDROME

- Inheritance is usually sporadic

Clinical findings

- At birth—small for gestational age, elfin facies with prominent lips, feeding problems, failure to thrive, hypercalcemia, hypercalciuria, developmental delay.
- Cardiac disease includes supravalvular aortic stenosis (most common), supravalvular pulmonic stenosis, and hypertension.
- Irritability in infancy and mildly obsessive behavior in childhood.
- Older children may develop diabetes mellitus, sensorineural hearing loss (hyperacusis), abnormality in spatial relations and abstract thinking, attention-deficit hyperactivity disorder, phobias.
- Williams syndrome children may have excellent vocabularies and unusual musical skills such as perfect pitch (friendly personality).

Diagnosis

- Typical facies and hypercalcemia at birth are often the first clue.
- FISH technology reveals the chromosomal deletion.
- The defect is on chromosome 7.
- Most cases are new mutations.
- Hypercalcemia and hypercalciuria may be absent or of very short duration and always resolve by age 2 years.
- Genetic evaluation should be performed in infants with phenotypic features even if the calcium is normal.

VACTERL ASSOCIATION

CASE

A 3 days old newborn presents with the complaint of not passing stool since birth. X-ray abdomen shows absence of gas shadow in rectum (imperforate anus). There is also a heart murmur on auscultation (VSD).

- VACTERL association is described by:
    - **V**ertebral defects (segmentation anomalies)
    - **I**mperforate anus
    - **C**ardiac malformation (most often ventricular septal defect)
    - **T**racheo-**e**sophageal fistula
    - **R**enal anomalies
    - **L**imb (most often radial ray) anomalies
- The disorder is sporadic.
- Some of the defects may be life threatening.
- The prognosis for normal development is good.
- Careful examination and follow-up are important, because numerous other syndromes have overlapping features.

CHARGE SYNDROME

- CHARGE syndrome affects structures derived from rostral neural crest cells but also includes abnormal development of the eyes and midbrain.
- Diagnosis is made if four of the major criteria (given below) are present, one of which should be either coloboma or choanal atresia.
- CHARGE syndrome include:
    - **C**olobomas
    - Congenital **h**eart disease
    - Choanal**a**tresia
    - Growth **r**etardation
    - **G**enital abnormalities (hypogenitalism)
    - **E**ar abnormalities, with deafness
- Choanal atresia may be unilateral or bilateral with a bony or membranous septum.
- Bilateral choanal atresia usually presents in the newborn period with obstructed breathing.
- Facial asymmetry is a common finding.
- Association is with mental retardation.
- CHARGE is now known to be caused by mutations in the *CHD7*gene on chromosome 8q.

PIERRE ROBIN SEQUENCE (SYNDROME)

CASE

A newborn presents with respiratory difficulty and is not taking feed properly. On examination, he has micrognathia, glossoptosis and cleft palate.

- Physical signs are micrognathia (mandibular hypoplasia), retroglossia (glossoptosis) and U-shaped cleft palate.
- It may be associated with congenital heart disease and feeding problems.
- There is sporadic inheritance.
- Airway obstruction may result from the tongue falling back into the pharynx (glossoptosis). Tracheostomy sometimes required.
- The sequence is associated with conditions that cause compression or decreased movement in utero.
- Prognosis is good if feeding and breathing difficulties are managed appropriately.
- Jaw growth occurs over initial years of life.

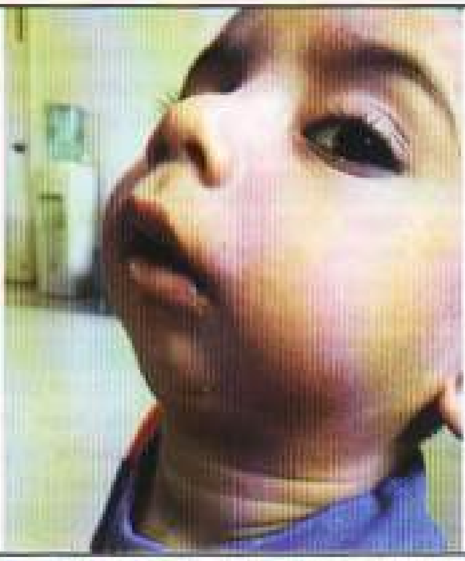


Fig 22.24 : Short chin Micrognathia

CHAPTER 23

Nephrology

Laboratory Evaluation of renal Function

Urinalysis:

- Urinalysis is simple, quick and inexpensive test and gives very important diagnostic information

Color:

- Depending upon the concentration, color varies from pale yellow to amber. Red, tea or cola colored urine suggest presence of blood, hemoglobin, myoglobin, porphyrin, beets or food color.
- Cloudy urine may reveal leukocytes, epithelial cells, bacteria, amorphous urates or phosphates.

Specific Gravity (SG):

- It usually ranges from 1.001 to 1.0035 and reflects the concentrating and diluting ability of the kidneys. Specific gravity may be converted to osmolality by multiplying the last 2 digits of SG by 40. e.g. SG of 1.007 means an osmolality of 280 mosm/kg.

pH:

- It usually ranges from 5.0 to 8.0 depending upon the acid-base balance of the body. It is important in diagnosing renal tubular acidosis (RTA) and monitoring in the treatment and prevention of urinary stones.

Glucose:

- Glucosuria is usually detected when plasma glucose is > 180-200mg/dl. However, it may be seen at lower glucose levels in isolated renal glucosuria or proximal tubular disorder such as Fanconi syndrome (FS).

Ketones:

- Ketones are detected in diabetic ketoacidosis, glycogen storage disease, starvation, high fats diet, and hyperthyroidism.

Proteinuria:

- Total urinary protein should be < 150mg/24 hours or <4mg/m^2/hr. More than 40mg /m^2/hr indicates proteinuria (nephrotic range). Spot urinary protein to creatinine ratio is also done to quantify proteinuria. Values of > 2mg/dl indicates nephrotic range proteinuria and < 0.2 is normal. Dipstick semi-quantitative proteinuria may quickly estimate as under:

  Trace or (±) = (10-29mg/dl)
  (+) = (30-100mg/dl)
  (++) = (100-300mg/dl)
  (+++) = (300-1000mg/dl)
  (++++) = (> 1000mg/dl).

Leukocyte esterase:

- Detected by dipstick and indicates presence of leukocytes/puss cell.

Nitrite Test:

- Detected by dipstick and indicates presence of bacteria capable of reducing dietary nitrate into nitrite such as E. Coli, Klebsiella, proteus, Citrobacter, Enterobatcter. For this to occur, urine must have remained in bladder for a minimum of 4 hours.

Urine Microscopy:

- It is extremely valuable in the evaluation of renal disease
- **Hematuria:** It is defined as the presence of > 5RBCs/hpf in a centrifugal urine. Dysmorphic RBCs suggest glomerular hematuria. RBCs casts are also pathognomonic of glomerular disease.
- **Plus Cells/Leukocytes:** More than 5 leukocytes/hpf of centrifuged urine may indicate urinary tract infection, especially if concomitant bacteriuria. White cell casts suggest acute pyelonephritis or acute interstitial nephritis.
- **Casts:** Hyaline casts are present in proteinuric states or in concentrated normal urine. Granular casts result from breakdown of cellular casts.

Crystals:

- Amorphous urates and phosphates are insignificant. Uric acid and calcium oxalate crystals may be seen in normal or pathological states. Hexagonal cystine crystals are pathognomonic of cystinuria.

Renal Function Tests (RFTs)

- RFTs include blood Urea Nitrogen (BUN), serum creatinine, serum sodium (Na), serum potassium(K), serum chloride(Cl), and serum bicarbonate (HCO_3).
- BUN may be converted into blood urea by multiplying with 2.14
- Blood Urea = BUN X 2.14
- Normal age ranges must be kept in mind for children.
- BUN = 10-20 mg/dl
- **Serum Creatinine:** Infant= 0.2-0.4 mg/dl
  1-2 years = 0.3-0.7mg/dl
- Serum sodium (Na) = 135-145mEq/L
- Serum Potassium (K) =3.3-4.6mEq/L
- Serum Chloride (Cl) =98-106mEq/L
- Serum Bicarbonate (HCO_3) = 21-28mEq/L

Estimated Glomerular Filtration Rate (GFR):

- GFR may be estimated by Schwartz formula:

$$GFR = k \times \frac{\text{height (cm)}}{\text{S. creatinine (mg/dl)}}$$

- K is a constant. The values of K varies:

Preterm Newborn = 0.27
Full term Newborn = 0.37
Infant = 0.45
1-12 years boys and girls = 0.55
Girls upto 18 years = 0.55
Boys upto 12-18 yrs. = 0.7

- GFR can be accurately measured by radionuclide diethylene pentaacetate (DTPA) renal scan.
- Cystatin C is, a new renal function test, independent of body muscle mass and better correlates that to GFR than serum creatinine.

  It can be estimated by enzyme immunoassay.
- Other Novel marks of RFTs: New biomarkers of RFTs under investigation include:

  Plasma neutrophil gelatinase-associated lipocalin (NGAL)
  Urinary NGAL
  Inter luekin 18
  Kidney injury molecule-1 (KIM-1)

Imaging of urinary Tract:

Ultrasonography:

- Ultrasound examination provides excellent information about the anatomy of urinary tract.
- It is noninvasive, painless, and requires no administration of contrast agent.
- It provides information about kidney location, size, shape and parenchymal thickness
- It can help diagnose obstruction, malformation, cysts, tumors, stones and nephrocalcinosis.

Plain Abdominal X-ray Film:

Helpful in detecting small renal and ureteric calculi and spinal evaluation in neuropathic bladder.

Micturating cystourethrography (MCUG):

- In this procedure contrast agent is instilled into the bladder through a catheter and x-ray films are taken when the child is voiding.
- It helps in diagnosis and evaluation of the severity of vesicoureteral reflux and detection of abnormalities of the bladder and urethra.
- With advent of fluoroscopy, the procedure is accomplished with lesser radiation close.

Radionuclide Scanning:

DTPA (Diethylene Penta acetic acid) renal scan:

- It provides estimation of GFR
- With post furosemide study, it helps in diagnosing obstruction.

DMSA (Dimercaptosuccinic Acid) Renal Scan:

- It helps to detect renal scars which are formed due to past episodes of pyelonephritis (shown as areas of decreased radiotracer uptake).
- It also helps locate ectopic kidney.

MAG3 (mercaptoacetyltriglycine) Renal scan:

- It is superior to DTPA scan in diagnosing obstructive uropathy

Intravenous Urography (IVU):

- Due to risk of contrast induced nephropathy, IVU is now replaced by much safer above mentioned radionuclide studies.

Computed Tomography (CT):

- Helpful in examining mass lesions of kidney, bladder or retroperitoneum that secondarily affect the urinary system.
- Radiation dose should be kept in mind.

Magnetic Resonance Imaging (MRI):

- MR urography in cases of hydronephrosis, duplex moiety and ectopic ureter.
- MR angiography in suspected renal artery stenosis.
- Limited use in children due to motion related problem and requirement of sedation.

Renal Biopsy:

- It is the definitive study for diagnosis of renal disease.
- The most common indications in children include steroid resistant nephrotic syndrome, lupus nephritis and other suspected glomerular and interstitial diseases.

Congenital Anomalies of the kidney and Urinary Tract(CAKUT):

Renal Agenesis:

- Complete absence of one or both kidneys.
- Bilateral agenesis not compatible with life.
- Unilateral agenesis may be associated with extra renal anomalies.
- Solitary functioning kidney is usually larger than normal.

Renal Hypoplasia:

- Small kidney without scarring on DMSA scan.
- Contralateral compensatory hypertrophy.

Renal Dysplasia:

- Multicystic Dysplastic kidney (MCDK) is a common anomaly.
- On ultrasound, renal parenchyma is replaced by non-communicating cysts of variable sizes.
- On DMSA or DTPA it is a nonfunctioning kidney.

- Contralateral kidney is usually normal, shows compensatory hypertrophy and is compatible with normal life.

Renal Ectopia:

- Ectopy may be simple (on the same side) or crossed (on the opposite side- crossed fused ectopia).
- Most common ectopic kidney pelvic
- Ectopic kidney usually has reduced function.

Duplex Kidneys:

- In complete duplication of ureter, the upper moiety is usually abnormal and lower moiety in normal.
- Patients with duplex kidneys are usually asymptomatic.
- However, UTI due to associated VUR or obstructive uropathy due to a ureterocoele may cause symptoms.

Pelviureteric Junction Obstruction (PUJO)

- May be detected on antenatal USG.
- Incidental detection of an abdominal mass, loin pain, hematuria or UTI are features in older children.
- USG and DTPA/MAG 3 establish diagnosis.
- Pyeloplasty is the treatment of choice.

Posterior Urethral Valves (PUVs):

- The most common cause of lower urinary tract obstruction in boys.
- Obstruction to the flow of urine causes dilation of the posterior urethra and hypertrophy of bladder neck.
- Bladder shows trabeculations, sacculations with varying grades of VUR.
- Recurrent infections lead to reflux nephropathy and chronic kidney disease (CKD).
- MCUG is the diagnostic test.
- Endoscopic resection / fulgaration the valve is the definitive procedure of choice.

Neuropathic Bladder

- Most common cause is spinal dysraphism (open myelomeningocele, spina bifida occulta, sacral agenesis etc).
- Risk of renal damage when sphincter detrusor dyssynergia(SDD).
- Socially unacceptable incontinence.
- There may be associated neuropathic bowel with chronic constipation/encopresis .
- MCUG is diagnostic.
- Clean intermittent catherization (CIC) is recommended in all cases.
- Anticholinergics e.g oxybutinin in cases with SDD.
- Urinary diversion procedures are often employed.

CLINICAL EVALUATION OF HEMATURIA

CASE

A 4-year-old previously well boy presents with an episode of frank ***hematuria***for 2 days. There is past history of ***lower abdominal pain***. There is no history of fever and dysuria. Physical examination is normal and urine dipstick showed microscopic hematuria 3+ and proteinuria 2+. Abdominal radiograph and ultrasound showed a ***calculus*** in the left kidney.

Definition

- Hematuria is defined as more than 5 RBCs per high-power microscopic field from a centrifuged clean-catch midstream freshly voided urine sample. RBC morphology is useful in distinguishing glomerular from non-glomeular causes of hematuria. Dysmorphic RBCs favour glomerular origin, while RBCs from lower tract maintain their morphology.
- Blood in the urine may be gross (visible to the naked eye) or microscopic (detected only by the dipstick or microscopic examination of the urine sediment).
- Two or more consecutive urine samples are more suggestive. The urine may be yellow, pink, red, brown, or smoky on gross examination.

Epidemiology

- Incidence: 0.17-0.3%
- Prevalence: 0.4–2.1% (microscopic hematuria)

Causes

Urinary Tract Infection (UTI)

- Bacterial
- Viral
- Fungal

Glomerular causes

Glomerulonephritis (GN)

Primary GN

- Acute postinfectious (poststreptococcal) GN
- Membranoproliferative GN
- Rapidly progressive GN
- IgA nephropathy (Berger disease)
- Membranous nephropathy

Secondary GN

- Systemic lupus erythematosus (SLE)
    - Henoch-Schonlein purpura

Other glomerular causes

- Hemolytic-uremic syndrome (HUS).
- Hereditary nephritis (Alport syndrome)
- Interstitial nephritis
- Thin glomerular basement membrane disease
- (Benign familial hematuria)

Stones

- Urolithiasis • Nephrocalcinosis
- Idiopathic hypercalciuria

Congenital abnormalities

- Polycystic kidneys (AR or AD)

Tumors

- Wilms tumor • Bladder Rhabdomyosarcoma
- Leukemias

Vascular

- Vasculitis syndromes • Renal vein thrombosis

Hematological

- Coagulopathies • Thrombocytopenia
- Sickle cell disease

Drugs

- Cyclophosphamide (Chemical cystitis)
- Salicylates • Sulfonamides • Anti-coagulants

Miscellaneous

- Trauma • Exercise induced
- Menarche (contamination of urine sample with menstrual blood)

Evaluation

- 'Tea or cola' colored urine is observed in acute glomerulonephritis but it may be bright red, suggesting more of an extra-renal or lower urinary tract source. Hematuria confined to the start or end of the urinary system also suggests lower urinary tract pathology.
- The presence of red urine but a negative microscopic examination and negative dipstick reaction for blood suggests that urine color is due to some food dye, rifampicin, desferoxamine administration, or urates, etc.
- If the urine tests positive for blood on dipstick but no red blood cells are seen on microscopy, the presence of free hemoglobin or myoglobin should be suspected.
- If a significant number of red blood cells are present but no casts are observed, it means that bleeding is below the glomerulus and renal tubules. The presence of red cells in the absence of casts is seen in some patients with hematuria associated with coagulopathy and after renal trauma. If the urine examination reveals the presence of hematuria and RBC casts, glomerular diseases should be considered, e.g. acute post-streptococcal glomerulonephritis, acute tubular or cortical necrosis.
- Painful hematuria may be due to direct injury to the urinary tract. Painful micturition (dysuria) is associated with cystitis or urethritis; loin pain is localized with acute pyelonephritis; or colicky radiating flank pain with a ureteric stone.
- Examining the morphology of the red blood cells is important. Altered red cells morphology is seen in glomerular hematuria, whereas in non-glomerular causes morphology is characteristically unaltered.

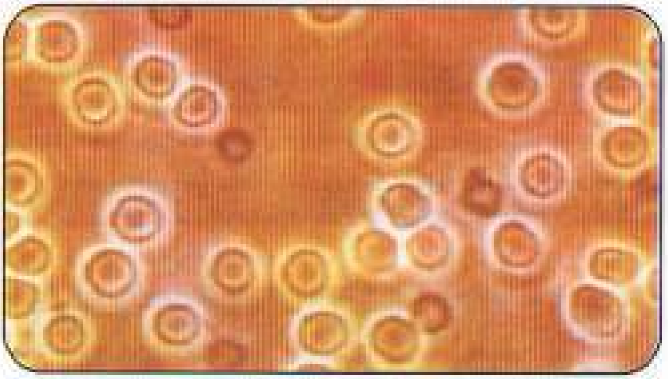


Figure 23.1: Microscopic picture of urine showing red blood cells

Diagnosis

Complete urine examination

- Dipstick: Detects hematuria, hemoglobinuria, myoglobinuria. Positive if 2 or more RBC/high power field.
- RBC Morphology:
  - Glomerular: RBC casts, damaged RBCs (dysmorphic, distorted, pitted, small)
  - Non-glomerular: Lack of RBC casts, normal looking RBCs
- Proteinuria: The presence of proteinuria (>1+ on dipstick) strongly suggests glomerulonephritis or intrinsic renal disease as the cause of hematuria.
- WBC, bacteria, crystals, pH

Urine culture and sensitivity (C&S)

Renal function tests

- Serum creatinine
- BUN
- Uric acid
- Ca/Cr ratio (hypercalciuria)

CBC with smear

- To rule out infection
- To rule out thrombocytopenia to exclude hemolytic uremic syndrome and Henoch-Schönlein purpura.

Bleeding profile

- Bleeding time (BT)
- Prothrombin time (PT)
- Activated partial thromboplastin time (APTT)

Serology

- Complement (C3, C4)
- ANA
- Anti- dsDNA antibody
- ASO titer

Imaging studies

- Renal ultrasound is indicated for:
- Gross hematuria
  - Suspected post renal anomalies
- To rule out congenital anomalies and Wilms' Tumor in young patients (less than 5 years of age)
- Micturitingcystourethrogram (MCUG) for suspected vesicoureteric reflux (VUR)
- IVU for imaging of collecting system, to detect stones and/or obstructive uropathy

Others

- Throat swab

- Renal biopsy
- Metabolic stone profile (24 hours' urine)

Management

- Treat underlying cause (Specific treatment)
- Treat associated complications such as hypertension, acute kidney injury, UTI, anemia etc.

IMMUNOGLOBULIN A NEPHROPATHY (BERGER DISEASE)

CASE

A 14-year-old boy presents with macroscopic ***hematuria*** and a ***rapid deterioration in renal function***. Percutaneous renal biopsy shows ***severe crescentic IgA nephropathy*** with extensive glomerular crescent formation.

- IgA nephropathy is the most common chronic glomerular disease in children.
- There is a predominance of IgA mesangial glomerular deposits in the absence of systemic disease.
- Diagnosis is confirmed on renal biopsy.

Pathology

- In glomerulus, there is focal and segmental mesangial proliferation and increased mesangial matrix.
- There are IgA deposits in the mesangium accompanied by C3 complement.
- IgA nephropathy is an immune complex disease.

Clinical findings

- IgA nephropathy is seen more often in male patients.
- Clinical presentation of childhood IgA nephropathy is often benign.
- It is an uncommon cause of end-stage renal failure during childhood.
- Microscopic or gross hematuria is common presentation.
- Patients may present with acute nephritic syndrome, nephrotic syndrome, or a combination of nephritic-nephrotic syndrome.
- Less commonly, a patient may present with a picture of rapidly progressive GN, as given in the box scenario above.
- Gross hematuria occurs within 1–2 days of onset of an upper respiratory or gastrointestinal infection.
- Proteinuria is often <1000 mg/24 hour.
- Mild to moderate hypertension may be present.
- There is normal serum levels of C3 in IgA nephropathy (low C3 is in poststreptococcal glomerulonephritis).
- Serum IgA levels are not diagnostic (elevated in only 15% of children).

Management

The primary treatment of IgA nephropathy is:

- Appropriate blood pressure control
- Management of significant proteinuria
- Angiotensin-Converting Enzyme (ACE) inhibitors are effective in reducing proteinuria. They decrease the rate of disease progression.
- Fish oil (contains anti-inflammatory omega-3 polyunsaturated fatty acids) may decrease the rate of disease progression.
- If above measures and ACE inhibitors are not effective or there is significant proteinuria, then immunosuppressive therapy with corticosteroids is recommended.
- Corticosteroids reduce proteinuria and improve renal function. Azathioprine or mycophenolate mofetil may be used along with corticosteroids in few patients. Patients with rapidly progressive GN/ crescentic GN need aggressive treatment.
- Tonsillectomy is occasionally used as a treatment for IgA nephropathy.
- Ultimate treatment is kidney transplantation in ESRD.

Prognosis

- Mostly, IgA nephropathy does not lead to significant kidney damage.
- Progressive disease develops in 20–30% of patients after 15–20 years of disease onset.
- Poor prognostic indicators are:
    - Persistent hypertension
    - Diminished renal function
    - Significant, increasing, or prolonged proteinuria.
- A more severe prognosis is correlated with extensive glomerular crescents, glomerulosclerosis, and diffuse tubulointerstitial changes (inflammation and fibrosis).

ACUTE POST-STREPTOCOCCAL GLOMERULONEPHRITIS

CASE

A 6-year-old boy presents with ***brown (dark) urine***. There is ***history of fever and a sore throat*** two weeks ago. He is afebrile but ***urine output*** is ***decreased***. On examination, he is active and non-toxic. There is ***periorbital edema***. Blood pressure is 140/90 mmHg (***hypertension***). Urine examination shows ***hematuria***and ***proteinuria***. Urine report also shows ***red blood cell casts*** under the microscope.

- Acute post-streptococcal glomerulonephritis is the most common form of immune-mediated nephritis in children.
- It is by far the most common form of postinfectious nephritis. It is characterized by sudden onset of hematuria, oliguria, edema, hypertension and deranged RFTs.

Etiology

- Post-streptococcal glomerulonephritis is a classical self-limiting illness resulting from a prior pharyngeal or cutaneous infection with group A beta-hemolytic streptococci. It may occur following otitis media or scarlet fever.
- Major differences in classical post-streptococcal GN following throat and skin infections are given in the following table.
- The attack rate of nephritis following nephritogenic strain of streptococci is 10–15%. Multiple cases tend to occur in families but second attack is rare.

Table 23.1: Major differences between Pharyngitis and Pyoderma.

	Pharyngitis	Pyoderma
Streptococcal type	Group A type 12 (4)	Type 49 (55)
Climate	Temperate or cold	Hot, tropical
Season	Winter and spring	Summer and fall
Age	5–10 years	Preschool (<5 years)
Incubation period	1–2 weeks	3-4 weeks
Sex incidence	Boys to girls 2:1	Equal in boys and girls

Pathogenesis

- This condition is thought to be an immune-complex mediated disease.
- An epidemiological relationship between certain strains of streptococci and glomerulonephritis is well recognized.
- Presumably antigen-antibody complexes are formed in the circulation and deposited in the glomeruli. These deposited complexes may incite glomerular damage through activation of the complement system.
- Pathologically, there is bilateral disease of the kidneys, which usually affect all glomeruli.
- On gross examination, the kidneys are swollen and have minute cortical hemorrhages.
- On light microscopy, there is swelling of the endothelial cells of the glomerular capillaries, proliferation of mesangial cells and polymorphonuclear cell infiltration. The proliferation of the outer layers of Bowman's capsule may lead to the formation of epithelial crescents.
- On electron microscopy, antigen-antibody complexes are seen to be deposited on the epithelial aspect of basement membrane and these deposits give granular appearance on immuno-fluorescence.

Clinical findings

- Acute nephritis is commonest in children between 5–10 years of age, and is quite rare before 3 years of age.
- Males are more commonly affected than females (3:2) in throat infection. Sex incidence is equal after a skin infection.
- There is usually a latent period of 3–4 weeks following a streptococcal infection of skin (impetigo) or 1–2 weeks following a respiratory tract infection (pharyngitis) or the infection may have passed even unnoticed.
- In a typical case, onset is abrupt with headache, malaise, and vomiting. There is passage of red or 'cola-colored' urine (in 30–50% of cases). The preceding tonsillitis or skin infection has been resolved by this time. Peri-orbital swelling (in 85% of cases) may occur especially in the morning but gross edema is unusual.
- The urinary output is decreased (below 180 ml/m2/day) and there is flank or midline abdominal pain.
- Acute hypertension (in 70% of cases) may cause headache, vomiting, altered sensorium, visual disturbances, aphasia, somnolence or even seizures (hypertensive encephalopathy in 5% of cases).
- Some patients may present with hypertensive heart failure or acute kidney injury (50%).

Natural Resolution

- The acute phase usually lasts 4–10 days when urine output gradually increases; edema subsides and RFTs return to normal.
- Gross hematuriaseldom persists beyond the 2 weeks but microscopic hematuria may persist for 1–2 years.
- Low grade proteinuria may be found up to 6 months after onset of AGN.
- Long-term prognosis is excellent. The incidence of CKD remains < 1% after APSGN.

Diagnosis

Urine examination

Complete urine examination reveals:

- Hematuriamay be gross or microscopic. Microscopy reveals dysmorphic RBCs and red cell casts. A considerable number of white blood cells may also be present in the urine.

- Variable proteinuria is present; usually less than 200 mg/dl.
- Specific gravity is more than 1.020, and Osmolality >700 mOsm/kg.

Blood examination

- ESR is raised.
- Hemoglobin level is decreased due to hemodilution.
- Total and differential leukocyte count usually remains within normal rage.

Complement (C3) level

- Complement C3 level is decreased (in> 95% of cases). It is low transiently and returns to normal in about 6-8 weeks.
- Failure of C3 to increase to the normal range beyond this period of time strongly suggests the diagnosis of membrano-proliferative GN, and a renal biopsy should be done for confirmation.

Evidence of streptococcal infection

- *Throat swab* for culture and sensitivity. Because about 20% of children are asymptomatic carriers of streptococci in the nasopharynx, one should not rely on a positive throat culture to diagnose post-streptococcal AGN.
- *Raised ASO titer*: Above 200 units/ml is suggestive. It is elevated in 80-90% of cases associated with antecedent pharyngitis. It may be < 50% positive in skin infections.
- *Streptozyme test:* Anti-DNAse B (anti-deoxyribonuclease B) and Anti-AHDase (Anti-hyaluronidase). Positive anti-DNAase B antibody is important if the preceding infection was pyoderma. Peak titers are reached 2–3 weeks after the infection and then they decrease.

Renal function tests

- Blood urea and creatinine levels are raised.

Serum electrolytes

- There is hyponatremia and hyperkalemia.

X-ray chest

- It may reveal cardiomegaly andperi-hilar infiltrates of pulmonary edema.

Renal biopsy

- It is rarely indicated, but should be considered when there is acute kidney injury, nephrotic syndrome, or persistent hypocomplementemia.

Management

- Early treatment of the streptococcal infection does not eliminate the risk of glomerulonephritis, in contrast to rheumatic fever. All therapy is supportive.

General/Supportive treatment

- **Bed rest:** Patient should be preferably hospitalized for close monitoring of BP and any derangement of RFTs and treatment of any complications as they arise.
- **Antibiotics:** The surviving hemolytic streptococci must be eradicated at the outset to prevent the spread of nephritogenic strains and prevent outbreaks in the community. Penicillin, the drug of choice, is given in the form of Benzyl Penicillin 5 lac units IM twice daily or oral Penicillin V 250 mg four times daily for 5–7 days.
- **Dietary restrictions:** Usually not desirable in pediatric practice in general, but these may be necessary:
  - Fruit juices should be avoided in order to limit potassium intake to not more than 30mEq/day.
  - If fluid overload, restrict fluid and give furosemide.
  - Sodium is given no more than 25mEq/day (1–2 g) especially if hypertension is present.
  - Calories: According to RDA but at least > 400/m^2/day as carbohydrate and fat to prevent tissue catabolism.

Treatment of complications

Anuria/severe oliguria

- Proteins should be completely withdrawn.
- Fluids given in the form of 10–20% glucose in water and should equal insensible water loss (400-500 ml/m^2/day) plus urine output. Calcium may be added to the iv fluids
- To prevent hyperkalemia withdraw potassium intake completely. If it develops, give treatment for hyperkalemia as given in the management of the acute kidney injury.
- Correct metabolic acidosis with sodium bicarbonate. This also helps in lowering serum potassium level.

Left ventricular failure

- Prop up the patient.
- Give moist oxygen.
- Restrict sodium and fluid intake.
- Give diuretics, e.g. furosemide (2-4 mg/kg/day).
- Control blood pressure (calcium channel blockers like amlodipine, beta blockers)
- Packed RBCs transfusion if anemia.
- Anuria beyond 2-3 days may require dialysis to manage fluid overload and electrolyte disturbances and to optimize nutritional support.

Hypertensive encephalopathy

- Inj. Hydralazine 0.1-0.5 mg/kg/dose iv 4-6 hourly or a continuous infusion (1-6 mcg/kg/min). It is contraindicated in CVA; so, rule out any focal neurologic deficit before giving hydralazine.

- IV furosemide 1-4 mg/kg/d in 2-4 divided dose
- Oral/NG amlodipine 0.1-0.5mg/kg/d OD
- Oral beta blockers like carvedilol (0.05- 0.5mg/kg/d OD), alpha blockers like prazocine (0.1-0.4mg/kg/d QID) may be needed in uncontrolled hypertension.
- ACE inhibitors like enalapril or ARBs(angiotensin receptor blockers) like losartan potassium are contraindicated in AKI. They may be used when renal function tests return to normal.

Differential diagnosis

- The following conditions may present as AGN:
- Membrano-proliferative glomerulonephritis
- IgA nephropathy
- Systemic lupus erythematosus
- Henoch-Schönlein purpura
- Vasculitis syndromes
- Infective endocarditis
- Shunt nephritis
- Other post-infectious GN e.g. Staph. aureus, Pneumococcus etc.

Prognosis

- Long-term prognosis in children is excellent.
- Complete recovery occurs in all children who survive acute stage although microscopic hematuria may persist for 1–2 years.
- About 1–2% children die during acute stage.
- Hypertension usually resolves within 3 weeks. Nearly 5% develop hypertensive encephalopathy.
- A small proportion of cases (<1%) will have persistent downhill course with proteinuria,hematuria and CKD.
- Second attacks are rare because there is paucity of nephritogenic strains of streptococci and lifelong type-specific immunity occurs.

HEMOLYTIC UREMIC SYNDROME

CASE

A 2-year-old previously healthy boy presents with ***pallor***. There is past history of ***bloody diarrhea*** one week ago. He is afebrile with a blood pressure of 150/100 mmHg (***hypertension***) and a heart rate of 130 beats per minute. On examination, he is pale, having ***pitting edema*** feet and scattered ***petechiae***. Laboratory investigations show hemoglobin of 8 g/dL, platelets 50,000/mm³, blood urea and creatinine of 60 mg/dL and 1.8 mg/dL, respectively.

- Hemolytic-uremic syndrome (HUS) is a common cause of acute kidney injury in young children.
- It is characterized by the triad of:
  - ○ Microangiopathichemolyticanemia
  - ○ Thrombocytopenia
  - ○ Renal insufficiency

Etiology

- The most common form of HUS (diarrhoea associated) is caused by Shiga-like toxin-producing *Escherichia coli* (STEC). Several serotypes of *E. coli* can produce the toxin e.g.O157:H7, O104:H4. *Shigellodysenteriae*type 1 is more common in our subcontinent.

Pathogenesis

- There is microvascular injury with endothelial cell damage. Capillary and arteriolar endothelial injury in the kidney leads to localized thrombosis, particularly in glomeruli. It is termed thrombotic microangiopathy (TMA).
- Progressive platelet aggregation in the areas of microvascular injury results in consumptive thrombocytopenia.
- Microangiopathichemolyticanemia results from mechanical damage to red blood cells as they pass through the damaged and thrombotic microvasculature.

Clinical findings

- HUS occurs a few days after onset of gastroenteritis with fever, vomiting, abdominal pain, and diarrhea.
- The prodromal intestinal symptoms may be severe or mild. Diarrhea is often bloody (but not always).
- Following the prodromal illness, there is sudden onset of pallor, irritability, weakness, and lethargy.
- Oliguria is present in early stages of HUS. Ongoing diarrhea may cause significant dehydration, or there may be volume overload due to renal insufficiency. HUS may be mild, or can progress to a severe and fatal multisystem disease. Renal insufficiency may be mild but can rapidly progress to severe oligo-anuric renal failure.
- Heart failure can be precipitated by volume overload, hypertension, and severe anemia.
- Severe CNS involvement (seizures and significant encephalopathy) occurs in ≤20% of cases. This is due to focal ischemia secondary to microvascular CNS thrombosis. Severe hypertension may also produce encephalopathy and seizures.
- Intestinal complications include severe inflammatory colitis, ischemic enteritis, bowel perforation, and intussusception.
- Patients can develop petechiae. But significant or severe bleeding is rare despite thrombocytopenia.

Diagnosis

- The diagnosis is based on the combination of:
  - ○ Microangiopathichemolyticanemia with schistocytes
  - ○ Thrombocytopenia
  - ○ Deranged RFTs.
- The anemia, initially mild, can progresses rapidly.
- Thrombocytopenia is usually 20,000–100,000/mm³.
- Partial thromboplastin and prothrombin times are norml. Leukocytosis is often present.

- Urinalysis shows microscopic hematuria and low-grade proteinuria.
- Renal insufficiency presents with elevations in serum blood urea nitrogen and creatinine.

Differential diagnosis

- Other causes of acute kidney injury associated with a microangiopathichemolyticanemia and thrombocytopenia:
    - Systemic lupus erythematosus
    - Malignant hypertension
    - Bilateral renal vein thrombosis

Management

- Main treatment is supportive care.
- Main aims of management are:
- Early recognition of the disease
- Monitoring for potential complications
- Meticulous supportive care
- Supportive care includes:
    - Careful management of fluid and electrolytes is necessary also including correction of volume deficit.
    - Hypertension should be controlled.
    - Early institution of dialysis if there is oliguria or anuria, particularly with hyperkalemia.
- Early intravenous volume expansion (before the onset of oliguria or anuria) may be nephroprotective.
- Red cell transfusions are required if there is significant hemolysis.
- Platelets are not given because they are rapidly consumed by the active coagulation. Despite thrombocytopenia, serious bleeding is very rare.
- Antibiotic therapy is not indicated because it can result in increased toxin release, exacerbating the disease.
- About 50% patients may require dialysis support during the acute phase of the disease.
- Plasma infusion or plasmapheresis may be used for patients suffering severe manifestations of HUS with serious CNS involvement.

Prognosis

- Most patients with diarrhea-associated HUS recover completely and there is little risk of long-term sequelae. Less than 5% patients remain dependent on dialysis. About 30% are left with some degree of chronic renal insufficiency. Patients with hypertension, any level of renal insufficiency, or residual urinary abnormalities persisting more than a year require careful follow-up.
- Patients who recover completely after a year are unlikely to manifest long-term sequelae. To exclude all late sequelae, annual examinations are needed.

Other infections causing HUS

- Neuraminidase producing **Pneumococcus** causing pneumonia, empyema, and bacteremia may lead to HUS. Coombs test is usually positive. Prompt treatment of pneumococcal infection is important. Plasma infusion or plasmapheresis is contraindicated.
- Untreated **HIV** infection may lead to a picture of TMA similar to HUS

Atypical HUS

- HUS not associated with diarrhoea is often labelled as atypical HUS (aHUS). Some important genetic or acquired causes are listed below:
    - Abnormalities of the complement system e.g. complement factor H, I deficiency etc.
    - von Willebrand factor-cleaving protease (ADAMTS 13) deficiency.
    - SLE
    - Malignant hypertension
    - Drugs e.g. cyclosporine A, clopidogrel
    - Cobalamin C deficiency
    - Post renal transplantation HUS
- The familial, genetic forms of HUS are progressive and/or relapsing and have poor prognosis.
- Plasmapheresis, and Eculizumab (an anti-C5 antibody that inhibits complement activation) show great promise in the treatment of atypical HUS.

HENOCH-SCHÖNLEIN PURPURA

CASE

A 7-year-old boy presents with ***abdominal pain*** and a ***rash mainly on the back of his legs and buttocks***.On physical examination, there is generalized abdominal tenderness, tender swelling of both ankles and knees, and a rash that ***do not blanch when pressed***. A complete blood count and urine analysis are normal. Prothrombin Time (PT), Partial Thromboplastin Time (PTT), and ***platelet counts are normal***. Blood urea and creatinine are also normal. Urinalysis shows hematuria and proteinuria. Stool is guaiac positive.

Henoch-Schönlein Purpura (HSP) or anaphylactoid purpura is the most common small vessel vasculitis in children.

- It is characterized by:
    - A purpuric rash
    - Arthritis
    - Abdominal pain
- About 50% of patients with HSP develop renal manifestations (asymptomatic microscopic hematuria or severe, progressive glomerulonephritis).

Pathogenesis

- There is deposition of polymeric immunoglobulin A (IgA) in glomeruli (glomerular findings can be indistinguishable from those of IgA nephropathy).

- The most common and earliest symptom is palpable purpura. It results from extravasation of erythrocytes into the tissue surrounding the involved venules.
- Antigens from group A β-hemolytic streptococci and other bacteria, viruses, drugs, food, and insect bites are some of the predisposing factors.

Clinical findings

- Skin rash may be urticarial initially, progressing to maculo-papules which coalesce to form symmetrical, palpable, non-blanching purpura mainly distributed on the legs, buttocks, and elbows. New skin lesions may continue to appear for 2–4 weeks. Skin rash may extend to involve the whole body.
- Some (about two thirds) of patients develop migratory polyarthralgia or polyarthritis (mainly of ankles and knees).
- About 50% of patients develop intermittent, sharp abdominal pain (due to hemorrhage andedema of the small intestine). Intussusception may develop.
- About 50% of those affected develop renal involvement after 2–3 weeks of illness (a nephritic or, less commonly, nephritic syndrome). Hypertension is main complication of renal involvement.
- Testicular torsion may occur.
- Neurologic symptoms may occur due to small vessel vasculitis.

Diagnosis

- Platelet count is normal or elevated.
- Other screening tests of hemostasis and platelet function are normal.
- Urinalysis frequently reveals hematuria. Sometimes, there is proteinuria.
- Stool may be positive for occult blood.

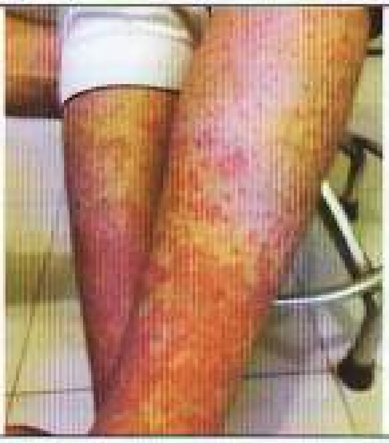


Figure 23.2: Characteristic rash Henoch-Schonlein Purpura (HSP).

- Antistreptolysin O (ASO) titer is often elevated.
- Throat culture may be positive for group A β-hemolytic streptococci.
- C3 level is normal.
- Serum IgA may be elevated.

Differential diagnosis

- Rash of septicemia (especially meningococcemia)
- Trauma
- Other vasculitides (lesions of thrombotic thrombocytopenic purpura are not palpable)

Management

- Generally, treatment is supportive.
- NSAIDs may relieve the pain of arthritis.
- Indications for using corticosteroids:
  - Severe gastrointestinal manifestations.
  - Orchitis
  - Severe renal involvement
- Penicillin is given if culture for group A β-hemolytic streptococci is positive or if the ASO titer is elevated.
- Mild HSP nephritis does not require treatment. It usually resolves spontaneously. KDIGO recommends using ACE inhibitors and/or ARBs for persistent proteinuria.
- Moderate or severe HSP nephritis requires treatment with high doses of corticosteroids, cyclophosphamide and azathioprine. Plasmapheresis and rituximab may have potential benefit. There is a high risk of progressing to CKD.

Prognosis

- Prognosis of HSP nephritis for most patients is excellent, although, symptoms frequently (25–50%) recur over a period of several months.
- Spontaneous and complete resolution of the nephritis occurs in majority of the patients with mild isolated hematuria and with insignificant proteinuria.
- Progressive renal failure occurs in less than 5% of patients with HSP. There is an overall fatality rate of 3%.

LUPUS NEPHRITIS

CASE

A 9 years old girl presents at OPD with passing cola colored urine and puffy face and eyes. There is history of off and on fever and pain knees and ankles for the last 2 months. On examination, BP is 140/100mmHg, and ankle edema is present. There is an obvious butterfly rash on her face. Laboratory workup reveals proteinuria, hematuria, deranged RFTs, low C3 and C4, normal ASO titer, and raised ANA and anti-double-stranded DNA antibody levels.

Upto 80% of children with lupus may have evidence of renal involvement at presentation. lupus nephritis is the most important cause of morbidity and mortality in SLE.

Pathogenesis

- Autoantibodies form immune complexes which are deposited in glomerular capillary endothelium with resultant complement mediated inflammation.

Clinical presentation

- The majority of children with SLE are adolescent females. The most common presentation is as nephritic or nephrotic syndrome with hypertension and impaired renal function. Less than 2% of patients may have a picture of acute kidney injury with rapidly progressive glomerulonephritis.

WHO classification of Lupus Nephritis

- Kidney biopsy remains the gold standard for establishing the diagnosis of lupus nephritis. WHO classification based on histopathology, immunofluorescence, and electron microscopy is useful to determine the selection of specific immunosuppressive therapies and to guide the patient and parents about prognosis. INSERT TABLE HERE.

Diagnosis

- The diagnosis of SLE is confirmed by detecting antinuclear antibody(ANA), low C3 and C4, and raised anti double stranded DNA antibody. Renal biopsy is performed in all patients to classify the disease severity.

Treatment

- The treatment of lupus nephritis depends on its severity. For class I and II, no specific therapy is required. In moderate to severe nephritis (Class III and IV), therapy is initiated with prednisolone 1-2mg/kg/d for 4-6 weeks and then gradually tapered to a maintenance dose of 0.2 to 0.3 mg/kg daily for 2-3 years or more. These patients are also given 5-6 monthly intravenous cyclophosphamide pulses at a dose of 500 -1000mg/m^2. Subsequently, cyclophosphamide is replaced by azathioprine (1-2mg/kg/d OD) or mycophenolate mofetil (25-30mg/kg/d in 2 divided doses). For class V nephritis, a combination of prednisolone and a calcineurin inhibitor (cyclosporine or tacrolimus) or mycophenolate mofetil is given. For patients presenting with AKI (rapidly progressive GN), 3-6 daily or alternate day pulses of intravenous methylprednisolone (15-20mg/g/dose) are used followed by oral prednisolone.

NEPHROTIC SYNDROME

CASE

A 4-year-old previously healthy boy presents with acute onset of ***facial edema*** and ***generalized swelling***. Examination reveals an afebrile child with a BP of 90/50 mmHg. He is alert with significant bilateral periorbital edema and pitting pedal edema. He has ascites with no organomegaly. His scrotum and lower extremities have tense pitting edema. On laboratory investigations, electrolytes, urea, and creatinine are normal. Urine dipstick shows ***protein 4+***. A 24 hours collection of urine reveals a protein excretion of ***2.5 g/24 hour***. There is also ***hypoalbuminemia*** and ***hypercholesterolemia***.

NEPHROTIC SYNDROME (NS)

- It is the most common renal disease in children
- It is characterized by
    - ✓ Progressive generalized edema
    - ✓ Heavy proteinuria > 1 g /m^2/ 24hr
    - ✓ Hypoalbuminemia < 2.5 g/dl
    - ✓ Hypercholesterolemia>220mg/dl

Classification According to response to Steroids

1. **Steroid Sensitive Nephrotic Syndrome (SSNS)** 85-90% NS patients who enter remission with corticosteroid treatment.
2. **Steroid Resistant Nephrotic Syndrome (SRNS)** 10-15% NS patients who fail to enter remission after 8 weeks of treatment with corticosteroids.
3. **Steroid Dependent NS (SDNS)** SSNS who relapse while patient is still on steroids(usually tapering dose) or within 2 weeks of stopping steroids
4. **Frequent Relapsing NS (FRNS)** SSNS who relapse 4 or more times in any 12 months period or 2 relapses in 6 months.
5. **Infrequent Relapsing NS (IRNS)** SSNS who relapse 1-3 times in any 12-months period or 1 relapse in 6 months.

Remission:

Urine dipstick proteinuria 0 to trace for 3 consecutive days with resolution of edema and normalization of serum albumin to at least 3.5 G/dl.

Relapse:

- Urine dipstick > 2+ for 3 consecutive days usually with recurrence of edema.

Classification according to age.

1. **Congenital Nephrotic Syndrome (CNS)** With onset at birth or before age 3 months
2. **Infantile Onset Nephrotic Syndrome (INS)** With onset between age 3 month to 12 months
3. **Childhood Nephrotic Syndrome** With onset between age 1 year to 12 years
4. **Adolescent Nephrotic Syndrome** With onset after age 12 years

Classification according to Etiology

1. Primary /Idiopathic Nephrotic Syndrome
2. Etiology unknown

Secondary Nephrotic Syndrome

- Secondary to some underlying external cause. All these classifications have therapeutic as well as prognostic implications.

Atypical features in Nephrotic syndrome

These may include one or more of the following;

1. Persistent microscopic hematuria or gross hematuria
2. Persistent low C3 level
3. Persistent hypertension
4. Deranged RFTs
5. Age< 1yr or >12years
6. External manifestation of a systematic disease

IDIOPATIC NEPHROTIC SYNDROME

- This is the most common type of nephrotic syndrome(NS) in children
- It accounts for about 90% of childhood NS.
- Overall incidence is between 2-6 cases per 100,000 children.
- It is more common in boys than girls (2:1) and typically occurs between 2-6 years of age.
- The disease is immune mediated and usually occurs after viral respiratory infections.
- **Primary histologic subtypes include:**
    - Minimal change Nephrotic Syndrome 75%
    - Focal Segmental Glomerulosclerosis (FSGS) 10% MCNS)
    - Mesangioproliferative Glomerulonephritis MesPGN)5%
    - Membranoproliferative Glomerulonephritis (MPGN) 4%
    - Membranous Nephropathy (MN) 1.5%
    - Immunoglobulin A Nephropathy(IgAN)
    - IgM Nephropathy.
    - C1q Nephropathy.

Pathogenesis (Mechanism of proteinuria)

- Glomerular capillary wall comprises 3 layers; an inner endothelial layer, a basement membrane and an outer epithelial layer composed of specialized cells called Podocytes. All 3 layers are negatively charged . Plasma albumin is also negatively charged. In nephrotic syndrome, due to loss of negative electrical charge on the basement membrane and epithelium, albumin is lost in urine.
- There is a generalized disorder of T-cell function which results in production of lymphokines which increase vascular permeability leading to proteinuria.
- In MCNS, proteinuria is selective; only albuminuria. In other lesions high molecular weight globulins are also lost in urine.

Pathophysiology:

- Edema is the cardinal feature of NS. There are 2 hypotheses of edema formation.

Underfill hypothesis:

- Heavy proteinuria is NS leads to hypoproteinemia and a fall in plasma oncotic pressure.
- Decrease in plasma oncotic pressure results in leakage of plasma water into the interstitium, producing edema.
- Resulting hypovolemia stimulates renin-angiotensin-aldosterone system (RAAS), release of antidiuretic hormonee (ADH) and inhibition of atrial natriuretic peptide (ANP).
- All these lead to salt and water retention further aggravating edema formation. MCNS better approximates to the underfill hypothesis.

Overfill hypothesis:

- In NS due to lesions other than minimal change, there is primary alteration in renal function causing salt and water retention, circulating volume expansion and an increase in plasma hydrostatic pressure leading to leakage of excess water into the interstitium.

Pathology:

Minimal Change Disease: 75%

- Glomeruli appear normal or show a minimal increase in mesangial cells and matrix.
- Immunofluorescence is normal.
- Electron microscopy shows fusion of epithelial foot processes.
- More than 95% children with MCNS respond to corticosteroids.

Focal Segmental Glomerulosclerosis (FSGS) 10%

- Glomeruli show sclerotic lesions that are both focal (present only in a proportion of glomeruli) and segmental (a portion of glomerulus).
- Immunofluorescence microscopy shows IgM and C_3 deposits.
- Electron microscopy shows segmental scarring of glomerular tuft with obliteration of capillary lumen.
- Only 20% patients with FSGS respond to prednisone.
- Disease is often progressive and leads to endstage kidney disease.

Mesangioproliferative GN:

- There is diffuse increase in mesangial cells and matrix
- Immunofluorescence might reveal IgM and/ or IgA deposits.
- Electron microscopy reveals increased mesangial cells and matrix as well as fusion of epithelial foot processes.
- About 50% respond to corticosteroids.

Clinical Findings:

- NS in children is most common between ages 2-6 years.
- MCNS is present in 85-90% in patients < 6 years of age. In contrast, in adolescents only 20-30% have MCNS. FSGS is more common in this older age group.
- Typically, the child develops periorbital swelling and oliguria follow flu like symptoms.
- Within few days edema becomes generalized when patient develops ascites, pleural effusion and scrotal

swelling in boys. There is often oliguria and mild abdominal pain.

- With marked generalized anasarca, there may be dyspnea.
- Blood pressure is often low normal.
- Occasionally, a patient may present with complications listed below.

Diagnosis:

- Dipstick proteinuria 3+ or 4 +
- Timed Urine collection: proteinuria > $40mg/m^2$/hour or >$1g/m^2$/24 hours
- Spot Urinary Protein: creatinine = > 2(mg/mg)
- Hypoalbuminemia < 2.5 g/dl
- Hypercholesterolemia > 220mg/dl

Pre requisites before starting steroid Therapy

- Rule out TB by tuberculin test and chest X-ray
- HBsAG, anti HCV and serum ALT levels.

Management:

General Management:

- Most patient can be managed as outpatients.
- Parental counseling is very important for best outcome. Tell them about the disease nature, its long duration, natural relapsing course, side effects of treatment and regular follow up.

Diet:

- Increase protein intake to 130% to 140% of the RDA for age.
- Avoid saturated fats that can worsen hyperlipidemia.
- Restrict salt intake to < 2g/day, No added salt is to be advised.

Diuretics:

- Not normally required. Injudicious use in all patients with NS may lead to grave complications such as shock, acute kidney Injury (AKI) and thromboembolism .
- Very cautions use may be needed when:
  - Severe generalized anasarca causing respiratory distress.
  - Imminent scrotal skin rupture.
- It is best to infuse salt free albumin 20% or 25% at a dose of 1 g/ kg along with furosemide in such situations.

Specific Management:

Treatment of initial episode of NS:

- In suspected MCNS, start with prednisolone $60mg/m^2$/day or 2 mg/kg/day (maximum 60 mg/day) for 4-6 weeks as a single morning dose after breakfast.
- If remission is achieved, prednisone 40 mg/m^2qod or 1.5 mg/kg qod is given for another 2-5 months, with tapering. A minimum total duration of treatment is 12 weeks.

Treatment of IRNS:

- Prednisone $60mg/m^2$/day or 2 mg/ kg/day until dipstick protein is –ve for 3 days.
- Then 40 mg/m^2/day or 1.5mg/kg/day on alternate days for 4 weeks, then stop.

Treatment of FRNS:

Continue infrequent relapse treatment for 3 months at lowest dose to maintain remission or use corticosteroid sparing agents like cyclophosphamide, levamisole, calcineurin inhibitors (cyclosporine A, Tacrolimus) or mycophenolate mofetil.

Treatment of SDNS:

Treatment duration is prolonged with lowest effective dose of prednisolone (0.25 mg/kg/day or < 0.5 mg/kg/qod) avoiding steroid toxicity. Steroid sparing agents as for FRNS are often utilized.

Adverse Effects of steroids:

- Cushingoid features and obesity
- Hypertension
- Growth retardation (Short stature)
- Behaviour changes like aggression, hyperactivity, sleep disturbances
- Increased susceptibility to infections
- Gastritis
- Osteoporosis and Osteopenia
- Posterior subcapsular cataracts
- Diabetes mellitus
- Benign intracranial hypertension
- Delayed wound healing
- Proximal myopathy
- Adrenal Suppression
- These side effects are to be kept in mind and countered whenever possible.

Complications of NS and their Management

Infections:

- NS patients are prone to significant infections due to defective humoral and cellular immunity as well as due to use of steroids.
- Always keep a high index of suspicion for infections as the child may be afebrile despite harboring severe infection.
- Common infections in NS include cellulitis, peritonitis, pneumonia, UTIs, and bacteremia.
- Chickenpox and shingles are medical emergency in children receiving immunosuppressive drugs.
- If an infection is suspected , a blood culture should be taken first and then empiric broad spectrum antibiotic therapy started.
- For spontaneous bacterial peritonitis, peritoneal fluid analysis, gram staining and culture should be done and broad spectrum antibiotics covering pneumococcus and gram negative bacteria started.

Thromboembolism:

- NS patients are prone to both arterial and venous thrombosis.
- Predisposing factors include:
  - Thrombocytosis and increased platelet aggregability
  - Increased clotting factors 5,7,8,10,1
  - Decreased antithrombin III.
  - Hypovolemia and increased blood viscosity.
  - Corticosteroid therapy.

- Injudicious use of diuretics.
- Treatment will include low molecular weight heparin, regular heparin warfarin, antiplatelet agents like clopidogrel, low dose aspirin.

Relapse with upper respiratory infection:

Most relapses are associated with viral respiratory infections.

If the child is already receiving alternate day treatment with steroids and develops URI with relapse of proteinuria, the same dose is given daily for one week and if remission is achieved, bring back to same alternate day dosage. If the child is off medications, prednisolone 0.5 mg/kg/day for one week is recommended to prevent relapse.

Home Monitoring of Proteinuria:

This is quite simple and cheap with urinary dipstick. The first morning specimen of urine is tested daily for proteinuria and a diary is maintained. This is very helpful to detect early relapse of proteinuria and thus to prevent relapse of the disease by giving daily prednisolone (0.5 mg/kg/d) for one week.

Calcineurin Inhibitors (CNIs)

Cyclosprin A:

- Dose is 4-5mg/kg/day (1000-150mg/m2 /d) in 2 divided dose
- Side effects: Nephrotoxicity (Monitor trough levels 8-150ng/ml)

  Cosmetic side effects e.g. Hirsutism, gum hypertrophy

  Others: Hypertension, hypercholesterolemia , tremors

Tacrolimus:

- Action is similar to cyclosporine
- Dose is 0.1-0.15mg/kg/d in 2 divided dose taken before meals.
- No cosmetic side effects and no lipid abnormalities but nephrotoxicity and hypertension are seen
- Other side effects include diarrhea , headache , high blood glucose level.

Mycophenolate Mofetil

- Dose is 30mg/kg/d (600-750 mg/m^2/d) in 2 divided dose taken before meals
- No nephrotoxicity or cosmetic side effects
- *May cause leucopenia , raised transaminases.*

Levamisole:

- Dose is 2-2.5mg/kg/day
- Effective in only FRNS and SDNS
- Side effects: GI upset , flu-like symptoms, transient leucopenia, skin rash

Inj. Rituximab:

- Anti CD 20 monoclonal antibody
- Two to four weekly doses (IV infusion 375mg/m^2)
- Rescue therapy in FRNS, SDNS and SRNS
- Long term safety is still to be established

Note:

Low dose alternate day prednisolone is combined with all these second line drugs.

Immunizations in children with nephrotic syndrome

- Vaccination reduces the risk of serious infections in nephrotic syndrome.
- Pneumococcal vaccination and influenza vaccination are indicated. Influenza vaccination is recommended annually to the children and their household contacts.
- Live virus vaccines should be deferred until the prednisolone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days.
- Live virus vaccines are contraindicated in children receiving cyclophosphamide or cyclosporine.
- Following close contact of child with varicella infection, varicella-zoster immune globulin is given. Healthy household contacts are immunized with live vaccines to protect the child with nephrotic syndrome from infection. Protect the child with nephrotic syndrome from direct exposure of gastrointestinal or respiratory secretions of vaccinated contacts for 3–6 weeks after vaccination.

Prognosis

- Many children with steroid-responsive nephrotic syndrome have repeated relapses.
- These repeated relapses usually decrease in frequency as the child grows older.
- Children who respond rapidly to steroids and children who have no relapses during the first 6 months after diagnosis usually follow an infrequently relapsing course.
- Child with steroid-responsive nephrotic syndrome is unlikely to develop chronic kidney disease.
- Children with steroid-resistant nephrotic syndrome (especially caused by FSGS) have a much poorer prognosis. They develop progressive renal insufficiency leading to end stage renal disease.

SECONDARY NS

Nephrotic Syndrome secondary to some underlying systemic disease, malignancy or drugs usually presents with atypical features like hematuria, hypertension, deranged RFT , hypocomplementemia and age > 8 years

Systemic Diseases:

- SLE
- HSP
- Hepatitis B virus
- Hepatitis C virus
- HIV
- Malaria

Malignancy:

- Hodgkin lymphoma
- Carcinoma lung
- Carcinoma GIT

Drugs + Chemicals:

- Penicillamine , captopril ,NSAID (cause membranous nephropathy)
- Ethosuximide, lithium , probencid (cause MCNS)
- Procainamide ,Chlorpropamide, Phenytoin (Cause MPGN)

Note: We have to find and treat the underlying cause only in secondary nephrotic syndrome. Omitting the suspected causative drug is necessary.

Congenital NS (NS)

CASE

A 2 months old male baby presents with decreased urine output and generalized body swelling. Urine examination shows 4+ protein.

- Nephrotic syndrome manifesting at birth or within first 3 months of life is called congenital nephrotic syndrome.
- Congenital nephrotic syndrome has a poorer prognosis.
- Congenital nephrotic syndrome may be classified as primary or as secondary.
- Primary congenital nephrotic syndrome is due to some syndromes inherited as autosomal recessive disorders.
- Secondary congenital nephrotic syndrome may be caused by:
    - In utero infections (cytomegalovirus, toxoplasmosis, syphilis, hepatitides B and C, HIV)
    - Infantile systemic lupus erythematosus
    - Mercury exposure
- Affected infants with congenital nephrotic syndrome present at birth with:
    - Edema caused by massive proteinuria
    - An enlarged placenta (>25% of the infant's weight)
- There is severe hypoalbuminemia, hyperlipidemia, and hypogammaglobulinemia.
- Prenatal diagnosis of congenital nephrotic syndrome can be made by the presence of elevated α-fetoprotein levels (maternal and amniotic).
- **Denys-Drash syndrome:**
    - There is abnormal podocyte function.
    - Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.
- **Pierson syndrome:**
    - Patients present with congenital nephrotic syndrome and bilateral microcoria (fixed narrowing of the pupil).
- **Diagnosis of congenital nephrotic syndrome is made clinically by:**
    - Severe generalized edema.
    - Poor growth and nutrition with hypoalbuminemia
    - Increased susceptibility to infections
    - Hypothyroidism (from urinary loss of thyroxin-binding globulin)
    - Increased risk of thrombotic events
- Most infants have progressive renal insufficiency.
- Secondary congenital nephrotic syndromecan be treated by treating the underlying cause, such as syphilis.
- Management of primary congenital nephrotic syndrome includes:
    - Intensive supportive care with intravenous albumin and diuretics
    - Regular administration of intravenous □-globulin
    - Aggressive nutritional support
    - Make effort to decrease urinary protein loss with angiotensin-converting enzyme inhibitors, angiotensin II receptor inhibitors, and prostaglandin synthesis inhibitors.
    - If above measures fail then unilateral nephrectomy is indicated.
- Bilateral nephrectomies and chronic dialysis is indicated if conservative management fails and patients suffer from persistent anasarca or repeated severe infections.
- Renal transplantation is the definitive treatment of congenital nephrotic syndrome.
- Congenital NS patients are universally hypothyroid due to loss of thyroxin globulin (TBG) in urine. Therefore, all CNS patients are given thyroxin replacement therapy.
- Vaccination: No vaccination is advised in CNS as all formed globulins are lost in urine.

INFANTILE NS (INS)

- When NS onset is between 3 months to 12 months of age , it is labeled as infantile NS. Rare syndromic forms and autosomal recessive FSGS and autosomal dominant FSGS may have infantile onset. They are all steroid resistant forms. Few INS patients may have MCNS and MesPGN and may respond to prednisolone
- Initial renal biopsy is recommended in all INS patients.

Adolescent NS

- First episode of NS after 12 years of age is labeled as adolescent NS. Initial renal biopsy is recommended. Membranous nephropathy and MPGN are more common at this age. The mainstay of treatment is ACEI or ARB for initial 6 months. If high grade proteinuria persists, CNIs, MMF or rituximab may be considered. If however biopsy shows childhood lesions like MCNS, MesPGN or FSGS, the same protocol of treatment as of children of younger age group.

Steroid Resistant Nephrotic Syndrome (SRNS)

- Renal biopsy is recommended before starting specific therapy.
- Most patients have FSGS (80%) followed by MesPGN, MCNS and MPGN.
- There is 50% risk of progression to ESKD within 5 years of disease onset.
- Calcineurin Inhibitors (CNIs) (cyclosporine and tacrolimus) are recommended as initial therapy
- Mycophenolate Mofetil has been shown to be effective in some patient.
- Strict control of hypertension is very important to prevent progression to CKD
- ACE inhibitors like enalapril and ARBs like losartan potassium may be given as an adjunct to reduce proteinuria in SRNS

Alternative Therapies in the treatment of NS

Alternative therapies are given in FRNS, SDNS and SRNS patients.

Cyclophosphamide:

- Effective in FRNS and SDNS to prolong remission and reduce the number of relapses.
- Dose is 2-2.5mg/ kg/day, single daily dose for 8-12 weeks (Total cumulative dose should not exceed 150-170mg/kg.)
- Main side effects include neutropenia, hemorrhagic cystitis , alopecia ,sterility, increased risk of future malignancy
- During treatment with cyclophosphamide white cells count should be monitored weekly, if the counts falls below 5000/mm3, drug should be stopped.
- Encourage increased fluid intake to prevent hemorrhagic cystitis.

Acute kindney Injury : (AKI)

CASE

A 4-year-old girl presents with history of ***anuria***, dysuria and abdominal pain of 24 hours duration. There is now frank ***hematuria***. On examination she is pale. Blood pressure is 120/80 mmHg (***hypertension***). Plasma sodium is 139 mmol/L (***hypernatremia***), potassium 6 mmol/L (***hyperkalemia***), chloride 100 mmol/L, bicarbonate 18 mmol/L (***metabolic acidosis***), ***urea*** and ***creatinine raised***. Abdominal radiograph reveals ***calcification*** in both kidneys. Abdominal ultrasound shows left-sided hydronephrosis and hydroureter and multiple stones in both kidneys causing ***obstruction***.

- Prerenal AKI due to hypovolemia and superimposed sepsis may occur . Underlying lesion is usually acute tubular necrosis (ATN) .
- Complete recovery is the rule with prompt treatment

Shock:

- An occasional patient may land with hypoyolemic shock due to inappropriate high dose of diuretics. Urgent volume replacement is needed in such patient.

Hyperlipidemia:

- Dietary fat restricted to <30% of calories and saturated fats to < 10% of calories
- Hyperlipidemia resolves as the patient goes into remission

Malnutrutim:

- This is common SRNS and frequent relapsers due to heavy protein losses
- Muscle wasting is masked by edema
- High protein diet is recommended throughout the treatment course.

Osteoporosis:

Vitamin D supplementation (e.g. cholecalciferol) and calcium supplements are often needed to minimize osteoporosis

Gastritis: Give H2 blockers, proton pump inhibitor or antacids along with prednisolone to prevent this complication.

Acute Kidney Injury: (AKI)

Formerly called acute renal failure, acute kidney injury (AKI) is a clinical state when sudden deterioration in kidney function results in the inability of the kidneys to excrete nitrogenous waste products and there is disturbance of fluid and electrolyte balance.

Acute kidney injury network (AKIN) categorizes the severity of AKI by rise in serum creatinine above the baseline:

Stage 1= Serum creatinim >1.5 times normal
Stage 2 = Serum creatinim >2 times normal
Stage 3 = Serum creatinim >3 times normal

Acronym RIFLE stands for Risk , Injury , Failure , Loss and End- stage renal disease.

Modified pediatric RIFLE (p RIFLE) Criteria:

CRITERIA Estimated CCL Urine output

Risk	eCCL decrease by 25% < 0.5ml/kg/hour for 8 hours
Injury	eCCL decrease by 50% < 0.5ml/kg/hour for 16 hours
Failure	eCCL decrease by 75% <0.3ml/kg/hour for 24hours Or eCCL 35ml/min /1.73m2 or anuric for 12 hours.
Loss	Persistent failure >4 wk
End-stage	Persistent failure > 3 mo

CCL = creatinim clearance (or GFR) eCCL = estimated creatinine clearance

Etiology:

AKI is classified into 3 categories according to the cause of AKI prerenal , intrinsic , and postrenal

Prerenal causes: Prerenal AKI occurs when there is inadequate renal perfusion due to:

- Diminished intravascular volume e.g. dehydration due to vomiting , diarrhea , hemorrhage, diabetic ketoacidosis , burns
- Decreased effective renal perfusion in heart failure and nephrotic syndrome
- Hypotension in septic shock
- Impaired renal blood flow due to drugs / radiocontrast agent e.g. cyclosporine, ACEI , ARBs.

Intrinsic Renal Causes:

- Glomerulonephritis
- Hemolytic Uremic Syndrome
- Acute Tubular Necrosis
- Renal vein Thrombosis
- Acute interstial Nephritis
- Tumor Lysis Syndrome
- Rhabdomyolysis (Crush injuries)

Postrenal causes:

- Posterior urethral valves
- Bilateral ureterovesical junction obstruction
- Neuropathic bladder
- Bilateral obstructive renal / ureteric stones
- Tumor obstruction
- Hemorrhagic cystitis

Pathohenesis:

Prerenal AKI:

Due to hypovolemia , hypotension or decreased effective blood flow , there is hypoperfusion of the kidneys which results in decreased GFR. Hypovolemia stimulates antidiuretic hormone (ADH) and aldosterone production resulting in oliguria and concentrated urine. AKI due to prerenal cause responds to early volume replacement, If renal hypoperfusion is prolonged beyond a critical point , intrinsic renal damage (acute tubular necrosis) occur.

Intrinsic renal AKI:

- Prolonged untreated prerenal failure leads to ischemic acute tubular necrosis (ATN)

- In hemolytic uremic syndrome (HUS) there is thrombotic microangiopathy (TMA) due to circulating Shiga toxin
- Untreated septic shock leads to ischemic as well as toxic ATN
- In acute glomerulonephritis (AGN) there is small vessel thrombosis by activation of coagulation system
- In acute interstial nephritis (AIN) there is a hypersensitivity reaction to a drug or infectious agent
- In tumor lysis syndrome, there is obstruction of renal tubules by uric acid crystals

Postrenal AKI:

- Bilateral urinary tract obstruction causes back pressure to the kidneys to cause AKI
- Relieving this obstruction is urgently required for a better outcome.

Clinical Findings:

- The child with AKI may have altered mental status and convulsions due to advanced uremia or hypertensive encephalopathy.
- Breathing may be rapid and deep from acidosis
- There may be peripheral or pulmonary edema.
- History of fluid or blood loss with severe dehydration (ATN)
- Edema , hematuria and hypertension (GN)
- Dysentery , pallor , petechiae (HUS)
- Sudden passage of dark red urine , pallor and jaundice (intravascular hemolysis e.g. malaria)
- History of interrupted urinary stream, palpable bladder (PUVS)
- Abdominal / flanks colic , hematuria , dysuria (Urinary tract calculi)
- Absolute anuria suggests urinary tract obstruction, ATN , bilateral renal vein thrombosis , severe GN or vasculitis
- Nonoliguric renal failure is seen in renal failure due to nephrotoxins. (e.g. Aminoglycosides, radiocontrast agents)
- AKI is sometimes superimposed on chronic kidney disease, growth retardation, renal osteodystrophy , anemia (CKD) and small shrunken kidney on ultrasound (normocytic ,normochromic) and suggest CKD.

Investigations:

- CBC with peripheral film may show microangiopathic hemolysis, thrombocytopenia and reticulocytosis in HUS.
- **Renal function tests (RFTs):** BUN, creatinine are raised.
- Serum electrolytes may show low sodium, high potassium, low calcium and high phosphate. Uric acid is always raised
- Throat culture, ASO titer and serum C3 level are examined in suspected acute GN.
- In glomerular and vascular disease, proteinuria > 1 g/m^2 /d along with red cells and casts may be seen.
- Eosinophils in the urinary sediment suggest interstitial nephritis.
- The presence of renal tubular epithelial cells, cellular debris and muddy brown tubular cells support the diagnosis of ATN.
- **Abdominal ultrasound:** It will reveal renal size, structural defects, hydronephrosis, hydroureter, stones and bladder anatomy.
- **Plain X-ray abdomen:** It may reveal stone, spinal abnormalities

MCUG:

It is diagnostic test in posterior urethral valves and vesicoureteral reflux.

X-ray chest: It may reveal cardiomegaly and pulmonary edema

Renal biopsy:

It is done in AKI when:

i. Etiology of AKI is not clear
ii. Unremitting AKI > 2-3 weeks where it may reveal crescentic GN or extent of renal damage e.g. ATN, cortical necrosis.

Management

General measures

- Establish a secure IV line.
- Draw blood samples for necessary investigations.
- Collect urine sample. Catheterize if bladder is palpable otherwise attach urine bag.
- Record blood pressure (one hourly if it is high; four hourly if it is normal).
- Careful intake and output record.
- Daily weight measurement.
- Urea, creatinine, serum electrolytes, and blood gases are estimated daily.
- Frequent ECG monitoring to detect hyperkalemia on time.
- In established renal failure, total fluid given per day is as follows:
- 400 ml fluid/m^2/day (insensible losses) + output (losses in urine, stool, vomiting)
- In infants 15 ml/kg fluid plus output (losses in urine, stool, vomiting) is given.
- Increase fluids by 10% for each 1°C rise in temperature.
- In general, glucose-containing solutions (10–25%) without electrolytes are used as maintenance fluids. The composition of fluid may be modified according to the state of electrolyte balance.
- At least 300 calories/m^2/day are given to reduce catabolism. Main part of calories should be from carbohydrates and fat. Protein should be restricted to 0.5 g/kg/day (1.0–1.5 g/kg/day in infants) of high quality protein such as egg, chicken, etc. Oral intake is more appropriate to avoid the fluid overload.
- Reversible conditions that can be treated should be given prompt attention. Obstruction of the urinary tract should be corrected or bypassed.

- Avoidance or careful monitoring of blood levels of drugs excreted by the kidney and appropriately adjusting either the total dose or the dosing interval are very important.

Fluid therapy

Renal failure with dehydration

- If a patient with renal failure is severely dehydrated or is in shock, IV fluid therapy is mandatory. Push normal saline 20 ml/kg within ½ hour.
- After ½ hour, observe for hydration status and passage of urine. If hydration and shock is improved, now give 90 ml/kg of normal saline or ringers lactate slow in 3 hours and again observe the hydration status and urine output.
- If there is no urine output after 3 hours and hydration is improved, give frusemide 2 mg/kg/dose IV stat and observe for 2–3 hours. If urinary output is not increased, a second dose of frusemide may be given. If still there is no urine output, peritoneal dialysis is indicated.
- If hydration is good but blood pressure is low, dopamine infusion is given to improve renal perfusion and blood pressure.

Renal failure with fluid overload (pulmonary edema)

- No IV fluids are given. Give frusemide 2 mg/kg/dose IV stat. Assess after 2–3 hours. Dose of frusemide may be repeated.
- If there is no diuresis after 2 doses of frusemide, a single IV dose of 0.5–1.0 g/kg of mannitol may be given over 30 minutes.
- Dopamine (5 μg/kg/minute) may be given if there is no hypertension; this will increase renal cortical blood flow.
- Peritoneal dialysis is indicated if there is no response to the above treatment.

Management of complications

Hyperkalemia

- Hyperkalemia is defined as serum level greater than 6 mEq/l.
- Medicines used to decrease the serum potassium when serum potassium rises above 7 mEq/l (but that do not affect the total body potassium) are:
  - Calcium gluconate (10%) at 0.5–1.0 ml/kg given IV diluted and slow over 10 minutes
  - Sodium bicarbonate 1–2 mEq/kg given slow IV diluted in normal saline.
  - Glucose solution (25%) 2 ml/kg given with regular insulin 1 unit/5 g of glucose given IV over 1 hour.
  - Procedure to deplete potassium stores includes the use of Kayexalate, either orally or per rectum, at the dose of 1 g/kg mixed with sorbitol. It is given for potassium levels of 5.5 mEq/l or more. It exchanges sodium for potassium.
  - β-adrenergic receptor agonists such as salbutamol given by nebulization also acutely lower potassium levels.
- The duration of action of the above measures is just a few hours. Dialysis is the only definitive therapy for removal of potassium.

Acidosis

- Partial correction of acidosis (to raise the arterial pH to 7.20, serum bicarbonate level to 12 mEq/l) is recommended by using the following formula:
  mEq/l $NaHCO_3$ required = 0.3 x weight (kg) x (12–serum bicarbonate, mEq/l)
- The remainder of the correction is made by the oral administration of sodium bicarbonate.

Hypocalcemia

- Hypocalcemia and hyperphosphatemia may present as tetany or convulsions. Give 0.5–1.0 ml/kg IV calcium gluconate slow and diluted in 5–10 minutes under cardiac monitoring.

Hyponatremia

- This usually occurs due to fluid overload or hypotonic fluid administration, therefore fluid restriction is indicated.
- Hyponatremia below 120 mEq/l may require correction (elevated to 125 mEq/l) with hypertonic sodium chloride:
- mEq/l of sodium required = 0.6 x weight (kg) x (125–serum sodium, mEq/l)
- When there is congestive cardiac failure and hypertension due to extreme fluid overload, this is a contraindication to hypertonic saline administration. In such situation, dialysis to correct hyponatremia may be required.

Hypertension

- Hypertension is a common complication in acute renal failure as a result of volume overload, primary renal disease, or both.
- Nifedipine or diazoxide are used in acute hypertension. In severe hypertension, continuous IV infusion of sodium nitroprusside is given. For chronic hypertension, propranolol or captopril is given.

Seizures

- This is a rare complication due to primary renal disease, uremia, hyponatremia, hypocalcemia, and hypertension.
- Diazepam is the drug of choice to control such seizures.

Infections

- Children with acute renal failure are susceptible to infections following bladder catheterization or peritoneal dialysis.
- Broad-spectrum antibiotics should be used and nephrotoxic drugs should be avoided.

Anemia

- This is a common complication (the result of volume expansion), but is mild and does not require treatment.
- If Hb falls below 7 g/dl, blood (pack cells 10 ml/kg) should be given very slowly in 4–6 hours.

- Blood should be fresh to decrease the amount of potassium administered.

Gastrointestinal bleeding

- This may be prevented by giving calcium carbonate antacids, or IV cimitidine (5–10 mg/kg/12 hour).

Dialysis

- If the oliguria is prolonged or clinical or metabolic deterioration occurs in spite of careful conservative management, then peritoneal dialysis or occasionally hemo-dialysis is required.
- Following are the indications for dialysis:
    - Hyperkalemia unresponsive to medical therapy
    - Acidosis unresponsive to medical therapy
    - Fluid overload unresponsive to fluid restriction or to diuretics
    - Symptoms and signs of uremia
    - Hypertension or congestive heart failure not responding to medical treatment
- Peritoneal dialysis is generally safe, simple and more effective.
- For peritoneal dialysis pediatric catheter is selected, bladder emptied and abdomen surgically prepared and catheter inserted 2 cm below the umbilicus in the midline under local anesthesia. The entire perforated segment of catheter must lie intra-peritoneally and catheter fixed with tape. A peritoneal dialysate is infused at a rate of 30 ml/kg and allowed to remain in peritoneal cavity for 30 minutes and allowed to drain in a bag by gravity method. If fluid is not recovered fully, then place the child in upright position at an angle of 45°. Dialysis is continued for 48 hours or rarely for 7 days and then catheter is removed. Start with isotonic fluids but if edema or fluid overload is present, alternate two cycles of isotonic with one cycle of hypertonic solution. Heparin can be added to dialysate to prevent clotting in the catheter (500 units/l solution). Antibiotics are added to the dialysis fluids; gentamicin 10 mg/l or cefotaxime 250 mg/l.
- The complications of catheter insertion and peritoneal dialysis are bleeding from insertion site, bowel perforation, peritonitis, respiratory distress, dehydration or hypervolemia, hyperglycemia, electrolyte imbalance, and failure to obtain adequate return of fluid.

Recovery phase

- Recovery from acute renal failure often involves a period of brisk urine output (diuretic phase or recovery phase of acute renal failure).
- This diuresis reflects excretion of water that accumulates in the earlier oliguric phase.

Electrolyte and fluid imbalance may occur in this phase.

Use of medications in AKI

- Avoid nephrotoxic agents eg aminoglycosides, NSAIDs, radiocontrast studies
- Avoid agents that reduce renal perfusion eg ACEI, ARBs
- Dose of agents medications should be adjusted according to GFR (usually taken as <15ml/min/1.73m^2) consult dose adjusting tables.
- Dopamine: Dopamine at low doses cause renal vasodilatation and may induce modest natriuresis.

Prevention of AKI:

- Prompt rehydration in acute diarrhea
- Judicious use of nephrotoxic drugs
- Careful hydration before radiocontrast diagnostic procedure
- Forced diuresis along with allopurinol to prevent AKI during tumors lysis (at start of chemotherapy)
- High index of suspicion in situations with high risk of AKI e.g post cardiac surgery, sepsis, ventilatory support, use of vasopressors and inotropes.

Prognosis

- Prognosis depends upon the cause. In patients with acute tubular necrosis, the period of anuria or oliguria usually lasts 7–10 days.
- Oliguria lasting longer than 3 weeks, or anuria, makes a diagnosis of acute tubular necrosis very unlikely.
- Prognosis is good (90% complete remission) in acute tubular necrosis, hemolytic uremic syndrome, and other causes responsible for prerenal failure.
- It is poor when renal failure results from rapidly progressive glomerulonephritis, bilateral renal vein thrombosis or bilateral cortical necrosis (less than 10% recovery), and may require chronic dialysis and eventual renal transplantation.

CHRONIC RENAL FAILURE (CRF) Chronic Kidney Di

CASE

A 10-year-old boy presents with ***growth failure***, headache, progressive ***pallor***, lethargy, anorexia, ***facial puffiness***, and bone and joint pain for last one year. On laboratory investigation, blood urea is 40 mg/dl, ***creatinine 7 mg/dl***, Na 146 mEq/l, K 6.5 mEq/l (***hyperkalemia***), Ca 8.5 mg/dl, PO$_4$ 10 mg/dl.

The term chronic renal failure (CRF) and chronic renal insufficiency (CRI) have now been replaced by more appropriate title of Chronic Kidney Disease (CKD)

Definition:

CKD is defined as evidence of kidney damage for >3 months or a decrease in GFR<6 ml/min/1.73m^2 for >3 months.

Evidence of kidney damage include:

- Albuminuria >30mg/24hr.
- Microscopic hematuria with abnormal urine sediment e.g abnormal RBCs morphology.
- RBCs, WBCs or granular casts
- Abnormal imaging e.g. polycytic kidney, dysplastic kidneys , hydronephrosis due to obstruction, cortical

scarring with vesicoureteral reflux, renal masses, renal artery stenosis, small hyperechoic kidneys.

- Abnormal histology e.g FSGS, lupus nephritis etc.

Staging of CKD:

This staging of CKD is proposed by National Kidney Foundation-Kidney Disease Outcome Quality Initiative NKF-KDOQI. CKD is classified into 5 stages based on GFR.

- **GFR is calculated by Schwartz formula:**

$$GFR(ml/min/1.73m^2) = \frac{Height(cm) \times K}{Serum\ creatinine\ (mg/dl)}$$

The 2012 Clinical practice Guideline of the Kidney Disease Improving Global outcomes (KDIGO) proposed a revised classification of CKD categories based on GFR, albuminuria and showing overall prognosis.

Table 23.2: Stages of chronic renal disease.

Stage	Residual Renal Function	Treatment Suggestions
Impaired renal function	40–80%	Usually not needed.
Chronic Renal Insufficiency (CRI)	25–50%	Any major stress may lead to acute renal failure. Aim of treatment is to preserve the renal function.
Chronic Renal Failure (CRF)	<30%	Aim of treatment is to prevent metabolic complications.
End-Stage Renal Disease (ESRD)	Usually <10%	Dialysis is needed to maintain quality of life.

Albuminuria is included as an additional risk factor because it marks the severity of injury and is associated with progression of kidney disease.

Causes of CKD:

Congenital anomalies of Kidneys and Urinary tract (CAKUT)

- Posterior urethral valves
- Renal hypo dysplasia
- Reflux nephropathy
- Bilateral pelviureteric junction or ureterovesical junction obstruction

Glomerular Disease

- **Glomerulonephritis:** Idiopathic, with SLE,HSP, Hepatitis B or C ,HIV
- Focal segmental Glomerulosclerosis (FSGS)
- Alport Syndrome
- Congenital Nephrotic Syndrome

Cystic Kidney Disease

- Nephronophthisis
- Autosomal recessive and dominant Polycystic Kidney Disease

Following AKI

- Hemolytic uremic syndrome
- Acute cortical necrosis

Tubulointerstitial Disease

- Inherited Cystinosis, primary hyperoxaluria, Barter syndrome, Dent, disease.
- **Acquired: Nephrolithiasis**
- There may be hyponatremia due to tubular damage or use of diuretics. Conversely, hypernatremia may be seen in aligoanuria.

Hypertension:

It is due to sodium and water overload and excessive renin production. It may cause hypertensive heart failure or seizures.

Bleeding Tendency

Main cause is defective platelet function and thrombocytopenia.

Uremic gastric ulceration and pericarditis are late features.

Uremic Encephalopathy

Infants and young children are more likely to develop encephlopathy due to high azotemia

Diagnosis of CKD

- Detailed history should be taken for main CKD systemic features.
- History to evaluate the etiology of CKD is to be individualized.
- Family history of renal disease should be obtained.
- Clinical examination should include measuring BP, weight and height, pubertal development . Anemia and features of MBD should be looked for.
- **Investigations assess the severity of CKD:**
- CBC with peripheral smear
- RFTs, Serum electrolytes, calcium, phosphate, alkaline phosphatase, total protein, albumin, uric acid.
- Arterial blood gases to look for blood pH and bicarbonate level.
- Intact PTH (fasting)
- X-ray left hand and wrist for bone age and MBD.
- Chest X-ray, ECG and echocardiography to assess left ventricular hypertrophy and function
- Calculate GFR by schwartz formula.

Specific Investigation

- These are to find out the cause of CKD and tailored to the suspected etiology e.g. ultrasound, KUB, MCUG, DMSA ,MAG3 or DTPA scans, urinalysis and urine culture, C3, C4, ANA, anti DNA antibody, renal biopsy, 24 hour oxalate level, white cell cysteine level etc.

Pathaphysiology and Systemic feature:

- Clinical features in advanced CKD (stage 3-5) include anorexia, growth failure, fatigue,anemia, hypertension and bone disease.
- The late feature (when GFR falls <15ml/min/1.73m^2) are itching,severe acidosis . hyperkalemia,left ventriculuar failure and pulmonary edema, pericarditis and altered sensorium.

Growth Retardation:

- Causes include poor nutrition (due to anorexia), metabolic acidosis, anemia and bone disease.
- Decreased growth hormone (GH) secretion and decreased insulin like growth factor(IGF)-I
- Secondary hyperparathyroidism: high PTH levels destroy growth plate architecture
- Delayed puberty is due to decreased gonadotrophins.
- Fluids and electrolyte losses in patients with renal dysplasia tubular disease also contribute to growth failure.
- Prolonged use of corticosteroids in glomerular disease also cause retardation of linear growth.

Anemia:

- Anemia causes easy fatigability and exertional dyspnea.
- Anemia is mostly normocytic and normochromic but superadded iron deficiency is often present.
- Main cause of anemia is lack of erythropoietin production.
- Other contributing factors include uremic bone marrow suppression, decreased RBC lifespan, iron and folate deficiency, and myelofibrosis.

Metabolic Acidosis and Dyselectrolemia:

- Metabolic acidosis is due to bicarbonate wasting, decreased acid secretion and decreased acid ammonia synthesis
- Acidosis leads to anorexia, vomiting and worsering growth failure.
- Hyperkalemia is a complication of advanced CKD.

Mineral Bone Disease (MBD)

- In CKD, when GFR declines to 50% of normal, there is decreased production of activated vit.D (1,25$(OH)_2$ cholecalciferol). This causes decreased intestinal absorption of calcium, hypocalcemia, increased PTH production and increased bone resorption
- Later, when GFR falls below 20-25% of normal there is decreased phosphate excretion from kidneys, resulting hyperphosphatemia further promotes hypokalemia and increase PTH secretion.
- Secondary hyperparathyroidism causes osteitis fibrosa cystica, bone resorption, fracture and deformities. Deficiency of 1,25 dihydroxy cholecalciferol leads to rickets/osteomalacia.
- Infants show rachitic rosary, widened wrist and knees, and Harrison sulcus.
- Older children show genovalgum, anterior bowing of tibia, scoliosis, thoracic abnormalities and pathologic fractures.

Management

- The aims of treatment in CRF prior to dialysis are to preserve any remaining renal function and to avoid and treat complications.

Nutritional management

- Inadequate caloric intake once renal function falls below 50% is a major cause of growth failure in children.
- Caloric intake of at least 100% of the Recommended Dietary Allowance (RDA) for age should be provided to children with CRF.
- Protein restriction is important in severe uremia. High biologic value protein (fish, chicken, eggs) is given 0.50–0.75 g/kg/day or 5% of total calories. In growing children 1.0–1.5 g/kg/day of protein is given to protect growth retardation.
- Caloric requirements are met primarily by carbohydrates (75%) and fats (20%).
- Milk intake can be reduced if there is phosphate overload.
- Water-soluble vitamins are recommended to avoid deficiency states.

Fluid balance

- Fluid restriction is rarely necessary in CRF as renal concentrating ability is lost unless oliguria or heart failure is present.
- When fluid is restricted, it should be sufficient to compensate for insensible losses (400 ml/m^2/day) plus losses in urine, vomitus, and stools.

Sodium balance

- Generally, no added salt in food is recommended. Most children with renal insufficiency will maintain normal sodium balance with sodium derived from diet.
- Patients with high blood pressure, edema, or congestive heart failure may need more strict sodium restriction.
- Poor weight gain and muscle cramps need sodium supplements. This is especially needed in some patients whose renal insufficiency is a consequence of anatomic abnormalities leading to sodium waste in urine.

Potassium balance

- This usually is not a problem in chronic renal failure, but hyperkalemia can be a potentially life-threatening situation.
- Avoid excessive use of high potassium food (banana, citrus fruits and juices, etc); restrict such food in a case of severe renal failure.
- Hyperkalemia may be controlled by adding oral alkalinizing agents and kayexalate (an oral resin that binds to and removes potassium from the intestine). It is given in a dose of 1 g/kg/dose.

Acidosis

- It develops in all children with CRF but treatment is required only if serum bicarbonate falls below 20 mEq/l.
- Sodium bicarbonate (soda mint) tablet may be given 1–2 tablets orally every 6 hours.

Anemia

- There is normocytic, normochromic anemia and it occurs mainly as a result of inadequate erythropoitin production. In addition, iron deficiency is also seen. Severe cases, requires blood transfusion (pack cells) given very slowly.
- The recent availability of recombinant erythropoitin has provided effective treatment for anemia.

Hypertension

- Blood pressure should be controlled gradually, but in hypertensive crisis nifedipine (0.25–0.5 mg/kg) should be given sublingually or diazoxide (hyperstat) 1–3 mg/kg IV.
- Routine treatment of hypertension includes salt restriction, diuretics, and beta-blockers. Captopril may produce hyperkalemia.
- When severe hypertension is associated with circulatory overload, 2–4 mg/kg of frusemide may also be administered along with the above treatments.

Drug dosages

- Renal excretion is a major route of excretion for many drugs; their dosages must be modified in chronic renal failure.

Renal osteodystrophy

- The plasma calcium and phosphate level should be kept as near normal as possible. Hyperphosphatemia should be controlled by giving low-phosphate milk and by giving oral calcium carbonate, which binds phosphate in the intestinal tract. It should be given with each meal and before going to bed.
- If serum calcium still remains low after correction of serum phosphorus, then oral calcium should be supplemented in a dose of 500–1000 mg/day.
- In addition, alfacalcidol (1 α Leo) may be given and regular monitoring of calcium level is done to prevent the risk of hypercalcemia. The dose is 0.05–0.10 μg/kg/day. The dose is progressively increased until serum calcium and alkaline phosphatase levels are normal and healing of rickets is seen radiologically. Then dose is reduced to initial level.

Infections

- Antibiotics are given to control infections especially UTI which is the most common infection in such patients.

Growth retardation

- In spite of adequate nutritional intake and correction of osteodystrophy, electrolyte abnormalities, acidosis, and anemia, many children with chronic renal failure have growth retardation.
- Growth in these patients may be accelerated with recombinant human growth hormone therapy.

Treatment of end-stage renal disease

- When the renal function is unable to sustain a stable milieu or serum creatinine is at 10 mg/dl, dialysis or renal transplantation is considered.
- The excretory function of the kidney can be partially replaced by peritoneal dialysis. It is only a holding measure until a suitable renal transplant becomes available. Continuous ambulatory peritoneal dialysis is the most common renal replacement therapy. Hemodialysis is another important method of replacing renal function.
- **Renal transplantation** has been very successful in children, even in those less than 1 year of age. Living related donor kidney transplantation has the best outcome.

Factors aggravating the pre-existing renal failure

- Uncontrolled hypertension
- Congestive heart failure
- Hypovolemia due to any cause
- Urinary tract infection
- Hypokalemia or hypercalcemia
- Nephrotoxic drugs
- Obstruction by renal calculus

Counseling and education:

- Parents should be informed about the nature of disease, role of preventive and therapeutic measures and likelihood of disease progression.
- The child should be encouraged to participate in activities and attend regular school. The need and availability of renal replacement therapy should be discussed in advance. Social support is also important.
- Immunizations : Ensure age appropriate immunization.

RENAL TUBULAR ACIDOSIS

CASE

A 5 month-old child has ***poor weight gain*** although his feeding is adequate. The child has had no illness, though mother noticed that baby is very thirsty, irritable most of the time and his pampers are too wet. The examination is normal except for the child's very low weight (failure to thrive). Laboratory investigations show normal blood counts. BUN and creatinine are normal. Serum electrolyte show sodium 137 mEq/l, chloride 110mEq/l, potassium 2.9mEq/l, and bicarbonate 17mEq/l. ***Urinalysis*** reveals a ***pH of 6.8, specific gravity 1.009***. Plain abdominal X-ray and renal ultrasound shows bilateral***nephrocalcinosis***.

Findings suggestive of Renal Tubular Acidosis (RTA)

- Growth retardation,Failure to thrive
- Polyuria
- Polydipsia
- Refractory rickets (usually proximal RTA)
- Renal calculi, nephrocalcinosis (distal RTA)
- Hyperchloremic, hypokalemic metabolic acidosis
- Hypercalciuria with normal serum calcium(distal RTA)

Types

- There are three types of renal tubular acidosis (RTA): distal (type I), proximal (type II), and hyperkalemic (type IV).

Distal RTA (dRTA)

- The most common form of distal RTA in childhood is the hereditary form.
- The clinical presentation is one of failure to thrive, anorexia, vomiting, dehydration and constipation. There is history of polyuria, polydipsia. An occasional patient may present with acidotic breathing.
- Work up reveals hypokalemia,hyperchloremia, metabolic acidosis along withhypercalciuria, nephrolithiasis or nephrocalcinosis.
- Patients with distal RTA cannot acidify their urine. They have a urine pH >5.8 despite a systemic metabolic acidosis.

Proximal RTA (pRTA) / Fanconi syndrome

- Proximal RTA is the second common form of RTA in childhood.
- It may be present in isolation.
- Mostly, pRTA is part of **Fanconi syndrome** (a generalized dysfunction of the proximal tubule) leading to:
    - Excessive bicarbonate loss
    - Glycosuria
    - Aminoaciduria
    - Excessive urinary losses of phosphate and uric acid
- The presence of a low serum uric acid level, glycosuria, and aminoaciduria is helpful diagnostically.
- Chronic hypophosphatemia leads to rickets in children.
- Rickets and/or failure to thrive may be the presenting complaint.
- The ability to acidify the urine is intact in proximal RTA. Thus, untreated patients have a urine pH <5.5.

Fanconi syndrome causes

- Important causes are as follows:

Neonatal

- Galactosemia
- Mitochondrial disorders
- Tyrosenemia

Infancy

- Fructosemia
- Cystinosis
- Faconi-Bickel syndrome
    - Lowe's syndrome

Childhood

- Cystinosis
    - Wilson's disease
    - Dent's disease

Acquired causes

- Aminoglycosides
- Sodium valproate
- FSGS
- Recovery phase of ATN
- Acute interstitial nephritis

Management

- Bicarbonate replacement is the main treatment.

- The dose of alkali required to achieve a normal plasma bicarbonate concentration in patients with distal RTA is low (usually 2–4 mEq/kg/day) in contrast to high dose that is required in proximal RTA (>10 mEq/kg/day).
- Serum bicarbonate should be monitored weekly until a level of at least 20 mEq/L is attained. Concomitant potassium supplementation may be needed especially in proximal RTA/ Fanconi syndrome.
- Citrate solutionsare somewhat more easily tolerated than sodium bicarbonate tablet. Total calculated dose is to be given in 4 divided doses daily.
- Bicitra solution contains 1mEq of Na and 1mEq of citrate(bicarbonate)/ml.
- Polycitra solution contains bicarbonate 2 mEq/ml, Na 1mEq/ml and K 1mEq/ml.
- Polycitra-K solution contains bicarbonate 2mEq/ml and K 2mEq/ml
- Patients with Fanconi syndrome also require phosphate supplementation for the treatment of hypophosphatemic rickets. This is given in the form of Joulie's solution which contains phosphate 30.5 mg/ml. At the same time, the underlying cause of Fanconi syndrome is also tobe diagnosed and treatment tailored accordingly.

Prognosis

- Prognosis is good in uncomplicated distal RTA when diagnosed early and treatment started properly.
- Correction of acidosis can result in reduced complications and improved growth.
- Prognosis is fair in proximal RTA. For Fanconi syndrome, the prognosis depends on the uderlying disorder or syndrome. Kids whose RTA is caused by a genetic defect may need treatment for the rest of their life.

BARTTER SYNDROME

CASE

An 8-month-old girl presents with ***failure to thrive*** and dehydration with polyuria. On examination, height and weight are less than the 5th percentile. On investigation, RBS is normal but there is hyponatremia, ***hypokalemia***, hypochloremia and ABGs show metabolic alkalosis. Urinary Ca, Na, K, Cl are increased. Plasma rennin activity and serum aldosterone are raised. ***Abdominal ultrasound shows bilateral nephrocalcinosis)***.

- Bartter syndrome is a group of disorders characterized by:
  - Hypokalemic,hypochloremicmetabolic alkalosis
  - Hypercalciuria
  - Salt wasting

Main clinical findings

- Failure to thrive
- Polyuria, polydipsia
- Recurrent episodes of dehydration
- History of polyhydramnios
- Hyponatremia (↓Na)
- Hypokalemia (↓ K)
- Hypochloremia (decreased chloride)
- Metabolic alkalosis
- Urinary chloride–increased
- Urinary Na, K, and Ca levels also increased
- Nephrocalcinosis (on abdominal ultrasound)
- Urinary Prostaglandin E2–increased
- Renin aldosterone–increased
- Blood pressure is normal

Diagnosis

- Diagnosis depends on clinical presentation and laboratory findings as above.

Differential diagnosis

- Gitelman syndrome occurs in older children and there are episodes of muscle weakness, recurrent tetany, hypokalemia, and hypomagnesemia. These children have hypocalciuria.

Management

- Treatment is directed towards replacing losses (fluids and electrolytes).
- Saline rehydration is urgently required when baby presents with dehydration.
- Correct hypokalemia with potassium supplements (KCl 1–3 mEq/kg/d PO divided TID or QID). Potassium supplementation, often at very high doses, is required.
- Sodium chloride supplementation
- Potassium sparing diuretics
  - Spironolactone (aldosterone antagonists) 2- 3 mg/kg/PO divided bid
- ACE inhibitors
  - Captopril 1-2 mg/kg/d PO TDS
- Indomethacin (prostsglandin inhibitors)
  - 2–3 mg/kg/day PO in divided doses
- Cyclooxygenase 2 inhibitors e.g. rofecoxib and renin inhibitors e.g. aliskiren may be required in few patients.
- GH for short stature (growth monitoring)
- Ca and Mg supplements if required e.g. muscle spasm or tetany

Prognosis

- Long-term prognosis is good if appropriate treatment is given for electrolyte balance, volume status, and growth.
- Some patients may develop chronic interstitial nephritis or chronic renal failure.

URINARY TRACT INFECTION (UTI)

CASE

A 3-month-old infant presents with ***fever***, vomiting and diarrhea. He is passing urine once a day in small amount for last many days. On examination, the infant is sick looking and dehydrated. Urine examination shows many ***pus cells***.

Definition

- UTI is defined as the culture of a pure growth of organisms >10^5 organisms/ml of urine sample.

Incidence

- UTI varies markedly with age and sex.
- UTI occurs in approximately 1–4/1000 of premature infants and newborns; many of these infections are hematogenously spread.
- In newborns, it is twice as common in boys; but in childhood, it is 10 times more common in girls.
- About 2.5% of school-age girls will have a UTI, and 80% of these patients experience a recurrence.

Localization

- A UTI is frequently classified based on involvement of the renal parenchyma (pyelonephritis) or the bladder (cystitis).
- Localization usually is based on clinical findings.
- Most infections do not involve the renal parenchyma.

Etiology

Common organisms are:

- Escherichia coli (75–90%)
- Klebsiella
- Proteus
- Staphylococcus saprophyticus
- Pseudomonas

Table 23.3: Clues to localize the UTI.

Signs or symptoms	Pyelonephritis	Cystitis
Fever >39°C	Common	Very unusual
Constitutional Symptoms	Common	Very unusual
Leukocytosis	WBC frequently >20,000	WBC usually normal
Elevated ESR	Virtually always	Unusual
Dysuria, frequency, urgency	Variable	Common
DMSA radionuclide scan	Areas of decreased uptake	Normal
Flank pain and costo-vertebral angle tenderness	Common (except in infants)	Absent

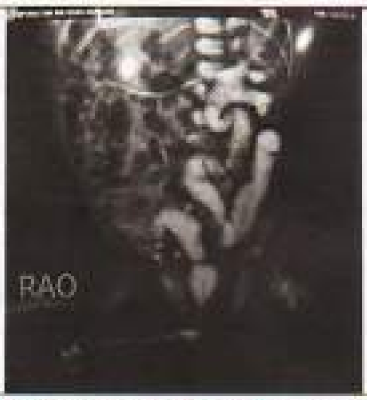


Figure 23.3 : Vesico ureteral reflux (Grade 4 reflux, left side.)

Pathogenesis

Contamination by fecal flora

- In virtually all cases, a UTI results from fecal flora, especially coliform bacteria, ascending the urethra to the bladder.
- Factors important to the development of UTI include:
    - The ability of organisms to adhere to the urinary epithelium
    - Urethral surface immunoglobulins (IgA)
    - Completeness of bladder emptying
    - Diabetes mellitus
    - Urine pH
- Pyelonephritis implies that organisms have ascended the ureters, as can occur in vesicoureteral reflux (retrograde flow of urine up the ureters from the bladder).

Vesicoureteral reflux

- VUR is present in 35% of children with a UTI.
- VUR definitely increases the risk of pyelonephritis.
- In most cases, VUR is caused by a congenitally abnormal insertion of the ureter into the bladder wall.
- Mild VUR may occur transiently with cystitis.
- Renal scarring is found in 50% of children with vesicoureteral reflux and infection. It is caused by reflux of urine into the renal parenchyma (intra-renal reflux). In most cases, such scarring occurs before age 2 years.

Grading of vesicoureteral reflux

Grade I:	Reflux into a non-dilated ureter.
Grade II:	Reflux into the upper collecting system without dilatation.
Grade III:	Reflux into dilated ureter and/or blunting of calycealfornices.
Grade IV:	Reflux into the kidney and grossly dilated ureter.
Grade V:	Massive reflux into the kidney, with ureteral dilatation and tortuosity and effacement of the calyceal details.

Other predisposing factors

- The problem of UTI is greatly aggravated by:
    - Poor hygiene
    - Constipation
    - Perineal infection (e.g. pin worms)
    - Stones
    - Instrumentation
    - Posterior urethral valves
    - Hydronephrotic kidneys
    - Abnormalities of collecting system
- In girls, short urethra also facilitates ascending infection.

Clinical findings

- Recognizing UTI in children, particularly in infants, may be difficult.
- **Newborn** may present with fever, hypothermia, poor feeding, vomiting, jaundice, failure to thrive, or sepsis.
- **Pre-school children** may have abdominal pain, vomiting, strong-smelling urine, fever, enuresis, increased frequency of urination, dysuria, or urgency.
- **School-age children** may develop the classic signs of UTI, including enuresis, increased frequency of urination, dysuria, urgency, fever, and costo-vertebral angle tenderness (flank pain). Occasionally, children with UTI present with hemorrhagic cystitis.
- Not all symptoms suggestive of UTI actually prove to be related to bacterial infection. Anatomic abnormalities producing voiding discomfort or irritation of external genitalia are examples of such problems. On the other hand, some UTIs may actually be relatively asymptomatic.

Diagnosis

Complete urine examination

- The presence of pyuria (>5 WBC/hpf) is suggestive of UTI but specimen collection is important.
- Pus in the urine does not necessarily mean acute UTI. Pus cells may be present in fever, dehydration, acute nephritis or contamination.
- Conversely, active UTI may be present without any pus cells in the urine in 50% of cases.
- Pyuria along with white cell casts is suggestive of infection.

Urine culture

- The diagnosis must be based on culture results.
- A count of 10^5 colony-forming units/ml for a single organism usually is accepted as proof of infection, although counts of 10^4 or less should not be discounted as contaminants.
- Falsely low colony counts are seen when morning specimen is not taken or the child is on antibiotics or the specimen gets contaminated with cleansing antiseptics.
- Repeat culture is required if symptoms do not improve within 48 hours of initiating antimicrobial therapy.
- Follow-up culture should be obtained at least 72 hours after completion of antimicrobial therapy.
- Methods of urine collection are:
    - Clean-catch, mid-stream samples can be 85% reliable
    - Sterile collection bag after disinfection of the skin of the genitalia
    - Catheterization and supra-pubic aspiration (in infants) are more specific means of obtaining samples, but these methods may cause discomfort and involve some risks

Nitrite sticks

- Non-culture methods such as nitrite sticks for early detection of UTI may be useful.

Imaging

- Ultrasonography should be performed to search for obstruction or urinary tract anomalies. It can be repeated serially to monitor renal growth.
- MicturatingCystourethrography (MCU) identifies vesicoureteral reflux and establishes the degree of reflux. The study is best performed after completion of therapy.

Renal function tests

- These are usually normal but in acute pyelonephritis there may be a mild and transient rise of blood urea and serum creatinine.

Management

- After UTI is confirmed, initial therapy should be based on the patient's history of antibiotic use, the location of the infection, and the subsequent drug sensitivities of the organism.
- Antipyretics are used for fever.
- High fluid intake is recommended.
- For uncomplicated cases of UTI, a single oral antibiotic that has not been used recently can be administered for 10–14 days. The choice of antibiotic therapy must be verified by prior culture and sensitivity testing.
- Oral antibiotics used in the treatment of UTI are:
    - Amoxycillin 20–50 mg/kg/day in 3 divided doses
    - Co-amoxiclave 20–45 mg/kg/day in 3 divided doses

  - Trimethoprim 8 mg/kg/day in 2 divided doses (for prophylaxis 2 mg/kg single daily dose)
  - Nalidixic acid 50 mg/kg/day in 4 divided doses (for prophylaxis 12.5 mg/kg single daily dose)
  - Nitrofurantoin 3–5 mg/kg/day in 4 divided doses (for prophylaxis 1 mg/kg single daily dose)
  - Cephradine 50 mg/kg/day in 2–4 divided doses
  - Cefixime 8 mg/kg/day once a day
  - Ciprofloxacin 250 mg BD for 7–10 days
- IV antibiotics used for pyelonephritis are:
  - For cocci (enterococci): Ampicillin 100–200 mg/kg/day in 4 divided doses
  - For Gram-negative rods (coliforms): Gentamicin 6 mg/kg/day in 2–3 divided doses, Ceftriaxone 50 mg/kg/day IV or IM in 2 divided doses.
- Antibiotic dosages are appropriately modified in patients with acute or chronic renal failure.
- Vesicoureteral reflux requires prolonged observation and medical management to which it often responds.

Preventive measures

- Risk factors for UTI should be investigated and eliminated.
- These factors include:
  - Congenital anomalies of the urinary tract
  - Conditions associated with incomplete emptying of the bladder (e.g. chronic constipation)
  - Habits that lead to chronic infection or irritation of the perineal area (e.g. wiping 'back to front')
- The child with VUR, other urinary tract anomalies, or a recurrent UTI requires continuous prophylactic antimicrobial therapy.
- Prophylaxis for recurrent UTI:
  - Trimethoprim 2 mg/kg orally in two divided doses Or
  - Nitrofurantoin 1–2 mg/kg orally at bedtime.

Complications

- Hypertension
- Renal scarring
- Severe vesicoureteral reflux
- Chronic renal failure

Follow-up

- All patients with UTI should be checked for recurrence every 1–2 months by urine culture until they have remained free of infection for 1 year.

Prognosis

- As long as UTI can be confined to the lower urinary tract (bladder and below), the prognosis is excellent.
- Once an infectious process has entered the kidneys, the prognosis becomes more guarded.
- Therefore, every diagnostic and therapeutic effort should be made to prevent recurrence.

HYPERTENSION

CASE

A 10-year-old girl presents with ***pallor, headache***, and dyspnea on exertion for the last three months. Her ***blood pressure is 180/120 mmHg***. Funduscopic examination shows ***hypertensive retinopathy***. Abdominal ultrasound showed ***small shrunken scarred kidneys.***

Definition

- Hypertension in childhood is defined as systolic or diastolic blood pressure reading greater than the 95th percentile for age, gender and height obtained on three separate occasions usually few weeks apart.
- The definition of normal blood pressure is systolic and diastolic blood pressure below the 90th percentile for age, gender, and height. Values between the 90th and 95th percentiles indicate prehypertension.

Incidence

- By above definition, approximately 1% of the pediatric population is hypertensive.

Etiology

Primary (essential) hypertension

- The term primary or essential hypertension implies that no known underlying disease is present. The prevalence of primary hypertension is increasing due to increasing obesity and sedentary life styles. Childhood onset essential hypertension is linked to essential hypertension later in life. Therefore, routine measurement of blood pressure in children is very important.

Secondary hypertension

- When the cause of the increase in blood pressure can be explained by an associated disease, the hypertension is called secondary.

Renal causes

- Different renal diseases account for the majority of secondary hypertension (75–80%).
- Virtually any renal disease, glomerular or interstitial, may be the cause.
- The hypertension may be transient or sustained and may be out of proportion in severity to the degree of renal insufficiency.
- Renal hypertension is caused by salt and water retention with volume expansion or by a renin-mediated increase in vascular resistance.

  - Congenitalanomalies (dysplastic kidney, polycystic disease, obstructive uropathy, reflux nephropathy)
  - Acute and chronic glomerulonephritis
  - Henoch-Schonlein purpura
  - Hemolytic-uremic syndrome
  - Wilms tumor

Drugs

- Steroids
- Cyclosporin

Neurologic causes

- Increased intracranial pressure
- Guillain-Barre syndrome
- Poliomyelitis
- Stress, anxiety

Endocrine causes

- Pheochromocytoma
- Cushing syndrome
- Hyperthyroidism
- Neuroblastoma

Vascular causes

- Coarctation of aorta
- Renal vein thrombosis
- Renal artery stenosis
- Takayasu'saortoarteritis

Monogenic causes of hypertension

- Liddle's syndrome (AD)
  - Apparent mineralocorticoid excess (AR)
  - Glucocorticoid remediable aldosteronism (AD)
- Gordon syndrome(AD)
  - Primary hyperaldosteronism (AD)
  - Congenital adrenal hyperplasia (AR)

History and examination

- Significant points to be asked in the history include:
  - Previous growth and state of health
  - Urinary tract symptoms and infections
  - Medications
  - Dietary intake
  - Level of activity
- Family history of hypertension, stroke or premature cardiovascular disease
- Blood pressure readings should be obtained when the heart rate is stable and repeated until values are consistent.
- Blood pressure readings should be obtained in all extremities, and pulses should be checked.
- Auscultation for murmurs and bruits and fundoscopic examination of retinal vessels are important.
- Falsely high blood pressure readings are frequently obtained when the size of the cuff is too small.
- An appropriate blood pressure cuff is the largest cuff that completely fits around the 2/3rdof upper arm. The inflatable bladder should almost completely encircle the arm.
- Blood pressure should be measured with the child lying or sitting comfortably with sphygmomanometer at heart level.
- The cuff should be inflated to approximately 20 mmHg above the point at which the radial pulse disappears.
- The recommended deflation rate is 2–3 mmHg per second while auscultation is performed over the brachial artery.
- Deflation that is too rapid or too slow will give inaccurate readings.Korotkoff phase 5 (complete disappearance of sounds) is used to indicate diastolic BP.
- Supine blood pressure value (mmHg) above the following should be regarded as indicating significant hypertension:

1 week–1 month	104 systolic
1 month–1 year	112/74
3–5 years	116/76
6–9 years	122/78
10–12 years	126/82
13–15 years	136/86
16–18 years	142/92

Clinical findings

- Hypertension is frequently discovered on routine examination of a patient who has no symptoms directly attributable to it. Symptoms, when they occur, result from complications.
- Hypertension may present with visual disturbances, headache, nausea, vomiting, heart failure, stroke, seizures, and coma.
- However, many patients are asymptomatic, which emphasizes the importance of frequently obtaining a blood pressure reading from every infant and child.
- Physical examination may be normal initially but with established hypertension changes occur in the optic fundi and evidence of left ventricular hypertrophy may become apparent.

Laboratory investigations

These depend on the underlying cause as evaluated by history and examination.

- Complete blood count
- Complete urine examination and urine culture
- Measurements of serum electrolytes (Na, K$^{Cl, HCO3}$)
- Blood urea and serum creatinine
- Serum uric acid

- Fasting lipid profile
- Chest radiograph
- Abdominal ultrasonography
- Electrocardiogram
- Echocardiography
- DMSA renal scan
- CT or MR angiography of aorta and renal vessels
- Measurement of hydroxy-methoxy-mandelic acid in 24 hours' urine (for pheo-chromocytoma, neuroblastoma)
- Plasma renin activity and serum aldosterone

Management

Initial therapy

- In mild hypertension, initial therapy should be non-pharmacologic i.e.
    - Reduction in salt intake
    - Weight reduction if indicated
    - Increased physical activity

Drug therapy

- It is given when the above measures are not sufficient.

Table 23.4: Anti-hypertensive drugs

Drug	Dose
Vasodilators	
Hydralazine	0.1-0.6 mg/kg/dose IV every4–6 hours 0.5–2.0 mg/kg PO every 6–8 hours. Maximum 200 mg/24 hours
Nitroprusside	0.5–8.0 mcg/kg/minute IV infusion
β-receptor blockers	
Propranolol (Inderal)	1-4mg/kg/d PO divided every 6–8 hours
Atenolol (Tenormin)	1-2 mg/kg/d OD
Alpha receptor blockers	
Prazosin (Minipress)	0.1-0.4mg/kg/d PO divided every 6 hours
Doxazosin (Cardura)	1-4mg/d PO OD
Sympatholytic agents	
α-methyl dopa (Aldomat)	10 mg/kg/d PO divided every 8–12 hours
ACE-inhibitors	
Captopril (Capoten)	0.5-3.0 mg/kg/d PO divided every 8 hours
Enalapril(Renitec)	0.2-1 mg/kg/d PO OD
Angiotensin receptor blockers	
Losartan potassium (Xavor)	0.8-1.8mg/kg/d PO OD
Calcium Channel Blockers	
Nifedipine (Adalat)	1-2 mg/kg/d PO divided every 6 hours. Sublingual preparation no longer used.
Amlodipine (Norvasc)	0,1-0.4mg/kg/d PO OD
Diuretic agents	
Furosemide (Lasix)	1-4mg/kg/d IV/PO divided every 6-12 hours
Spironolactone (Aldactone)	1-3mg/kg/d PO divided every 12 hours
Hydrochlorothiazide (Diuza)	1-4mg/kg/d PO divided every 12 hours

- Patients with essential hypertension may be treated initially with an ACEI or calcium channel blocker.
- Patients with volume-dependent hypertension usually respond adequately to diuretics; those with high-renin, high cardiac output physiology respond best to β-blockers.
- If the pressure is not lowered adequately, a calcium channel blocker may be added to the diuretic and an ACE inhibitor may replace the β-blocker.
- In patients with longstanding or poorly controlled hypertension, the underlying pathophysiology is often complex. Such patients frequently require trials of combinations of anti-hypertensive agents in order to gain control of markedly elevated or labile pressure.
- Therapy for secondary hypertension involves eliminating the cause when possible, and administering anti-hypertensive medication to stabilize the blood pressure and the patient.
- Angioplasty is indicated for coarctation of the aorta and renal artery stenosis. A nephrectomy may be indicated for a contracted scarred non-functioning kidney with normal contralateral one.
- Surgery is also definite treatment for pheochromocytoma. Prior to surgery, nifedipine, propranolol, and prazosin may be used to control BP in pheochromocytoma.

Treatment of hypertensive crisis

- A hypertensive emergency exists when central nervous system signs of hypertension appear, such as papilledema or encephalopathy. Retinal hemorrhages or exudates indicate a need for prompt and effective control. Hypertensive heart failure with pulmonary edema is also an emergency.
- Approximately a third of the desired reduction of BP is made over the first 8 hours with gradual normalizing theblood pressure over the following 24-48 hours, because too rapid reduction in blood pressure may lead to neurologic sequelae. The patient must be closely monitored during treatment to detect hypotension. Pupillary reaction to light should be frequently examined.
- Emergency medications are IV hydralazine, IV infusion of sodium nitroprusside or IV labetalol. If there is evidence of salt and fluid overload and patient is not anuric, IV furosemide should be administered.
- With control of hypertensive crisis, medications for sustained control of BP should also be initiated so that the effect will be maintained when the emergency measures are discontinued.

Prognosis

- The prognosis depends on the primary disorder.
- Uncontrolled essential hypertension does contribute to the cardiovascular, CNS, and renal morbidity.

URINARY LITHIASIS

CASE

A 4-year-old boy presents with ***acute severe pain*** in left lumbar region which radiate towards the left groin. He had had three similar episodes over the last six months. On examination, he is febrile, sick looking with BP 90/70 mmHg. His urine report revealed: Appearance slightly turbid, ***RBCs numerous/hpf***, WBCs 6–8/hpf, granular cast, ***oxalate crystals*** ++.

- Urolithiasis occurs following a complete interaction of environment and hereditary factors. Urinary crystals coalesce and precipitate when physical and biochemical conditions disturb the delicate balance of stone promoting and inhibitory factors.
- Urinary calculi consist of a very small glycoprotein matrix with surrounding organic or inorganic crystals.
- Urinary crystalloids capable of being crystallized include calcium, phosphorus, oxalates, cystine, uric acid, xanthine, and ammonium.
- Urine volume plays a critical role in determining the degree of saturation and spontaneous precipitation and crystal formation. Urine also contains inhibitors of stone formation that include citrate, diphosphonate, magnesium and zinc.
- Urine pH is an important factor in determining solubility. An acidic pH(<6) increases the solubility of calcium phosphate, and pH between 6-7 that of uric acid. An alkaline pH (>7.4) helps to keep cystine in solution.
- Calcium is a constituent of 90% of calculi (responsible for opacity on radio-graph). Calcium phosphate, the principal constituent of the calcium stones, is also found in struvite and other stones. Struvite stones (magnesium ammonium phosphate) often are called 'infection stones'.

Etiology

The occurrence of a stone in a child should be properly evaluated to determine the cause. An underlying metabolic cause is identified in a significant number of cases.

Calcium stones are most common (calcium oxalate and calcium phosphate);

- **Hypercalciuria:**
  - Hyperparathyroidism
  - Vitamin D intoxication
  - Neoplastic deposits in bones
  - Immobilization
  - Idiopathic or familial hypercalciuria
  - Distal renal tubular acidosis (type I)
  - Loop diuretic use
  - Thyrotoxicosis
  - Cushing's syndrome
- Hypercalciuria is the most common metabolic abnormality in calcium containing stone. 30–60% of children with calcium stone have calciuria without hypercalcemia. All above-mentioned conditions are responsible for hypercalciuria.
- **Hyperoxaluria: calcium oxalate stones**
  - Primary hyperoxaluria types 1 and 2
  - Inflammatory bowel disease (malabsorption)
  - Massive doses of vitamin C
- Hyperoxaluria is also an important cause of calcium stone because it increases the solubility product of calcium oxalate crystals. Primary hyperoxaluria is a relentless progressive disease leading to severe urolithiasis and systemic oxalosis. Secondary (enteric) hyperoxaluria occurs in inflammatory bowel disease, pancreatic insufficiency because unabsorbed fatty acids bind with calcium to form salts that are lost in stool. Normally, calcium forms a complex with oxalate to reduce oxalate absorption from gut. But if calcium

is unavailable, there is increased absorption of unbound oxalate.

Magnesium ammonium phosphate (struvite) and calcium phosphate (apatite) stones

- UTI with urea-splitting organisms (mostly Proteus). Stones are often staghorn shape.
- Theseare often seen in neuropathic bladder and pelviureteric junction obstruction leading to urinary stasis and infection.

Hyperuricosuria: Uric acid stones

- Leukemia-lymphoma
- Gout
- Lesch-Nyhan syndrome
- High purine diet
- Type I glycogen storage disease

Cystinuria: Cystine stones

- Cystine stone is an autosomal recessive disorder of the epithelial cells of renal tubule that presents with the absorption of four dibasic aminoacids (cystine, ornithine, arginine, and lysine) and result in excessive urinary excretion of these products. On urine examination, they have acidic urine and have hexagonal crystals.

• Primary xanthinuria: Xanthine stones

- **Idiopathic stones**
- **Nephrocalcinosis**:Nephrocalcinosis refers to calcium deposition within the renal tissue. Often nephrocalcinosis is associated with urolithiasis. The most common causes are:
- Furosemide (used in preterm newborns)
- Distal renal tubular acidosis
- Hyperparathyroidism
- Medullary sponge kidney
- Hyperoxaluria
- Hyperuricosuria
- Prolonged immobilization

Clinical findings

- Gross or microscopic hematuria may be the only manifestation, or hematuria may be accompanied by abdominal/flank pain or by fever, pyuria if superadded UTI.
- Typical colic is unusual in a young child but can be present in the older child.
- Stone or gravel may be passed spontaneously in some cases.
- Child may have a family history of stones.
- Urinary stones may cause obstruction of the urinary flow, dilatation of the urinary tract and ultimately renal parenchymal damage.
- Stones may predispose to UTI and UTI may predispose to stones.

Investigations

Blood:

- Urea, creatinine, electrolytes, pH, HCO_3, calcium, phosphorus, uric acid, magnesium, alkaline phosphatase, parathormone.

Urine:

- Urinalysis including urine pH, specific gravity
- Urine culture
- Spot urine for calcium/creatinine ratio
- Spot urine for cystine (cyanide-nitroprusside test)
- 24 hours urine for volume, sodium, creatinine, calcium, oxalate, phosphorus, citrate, magnesium, uric acid, and cystine.

Imaging

- Plain radiograph of the abdomen. All stones containing calcium are radiopaque. Cystine stones are slightly radiopaque because of the sulphur present in cystine. Struvite stones also are radiopaque. Uric acid stones are mostly radiolucent.
- Ultrasound of abdomen
- Intravenous Pyelogram (IVP)
- CT scan abdomen (preferably spiral)

Stone analysis: All passed stones or gravel must be tested completely for composition.

Management:

- One of the most important measures in preventing the formation or further growth of any stones, regardless of etiology, is to increase the urine volume by raising the fluid intake to 1.5 to 2 times normal (2400 ml/m^2/day or more).
- UTI, if present, must be treated.
- A search for anatomical abnormalities should be completed. Any urologic abnormalities predisposing to infections or stones should be corrected.

Stone removal

- Many small stones (< 6mm) pass through the urinary tract spontaneously.
- Some stones may dissolve slowly (e.g. uric acid stones) or at least may not grow with medical treatment.
- Some stones must be removed e.g. struvite stones, stones causing obstructive nephropathy, and stones causing chronic pain or resistant UTI.
- Removal by surgery or extracorporeal shock-wave lithotripsy is considered.

Specific therapeutic measures

- For **infective stones (struvite and carbonate apatite)**, treat UTI and correct underlying anatomic obstructive uropathy to prevent recurrence. Urinary acidification (rather than alkalinization) is required in these patients e.g. cranberry juice and vitamin C.

- The treatment for stones due to**hypercalciuria** includes restriction of sodium and animal protein intake. Dietary calcium restriction not recommended, since this might result in reduced bone mineralization and increased rik of enteric hyperoxaluria. Thiazide diuretics, which enhance renal tubular reabsorption of calcium, are quite effective in reducing calcium excretion and preventing recurrent stone formation.
- Allopurinol therapy is very effective in patients with **uric acid stones**. Alkalinization of the urine to a pH of >6.5 with sodium bicarbonate or sodium citrate is important in treating and preventing uric acid stones.
- Dilution of the urine decreases the saturation of **cystine** and alkalinization of urine (pH >7.5) will increase the solubility of cystine. D-penicillamine is another effective therapy because it is chelating agent that binds to cystine, increasing the solubility of the product. Tiopronin, N-acetylcysteine and captopril are also effective in the treatment of cystine calculi.
- Treatment of **primary hyperoxaluria** involves dual renal and hepatic transplantation because defective enzymes are hepatic, but ideally before renal failure.
- **Nephrocalcinosis:** Wehave to findand treat the underlying cause.
- **Distal RTA:** Sodium or potassium citrate therapy as discussed previously.
- Idiopathic calculi: Long-termtherapy with potassium citrate (2mEq/kg/day) along with increased fluid intake and restriction of salt and animal protein intake might be helpful.

CHAPTER 24

Dermatology

DEFINITION OF TERMS

Macule

- Flat, circumscribed area distinguished from surrounding skin by coloration. It is a color change but can be felt.
- When the lesion is larger than 1 cm, the term **patch** is used.

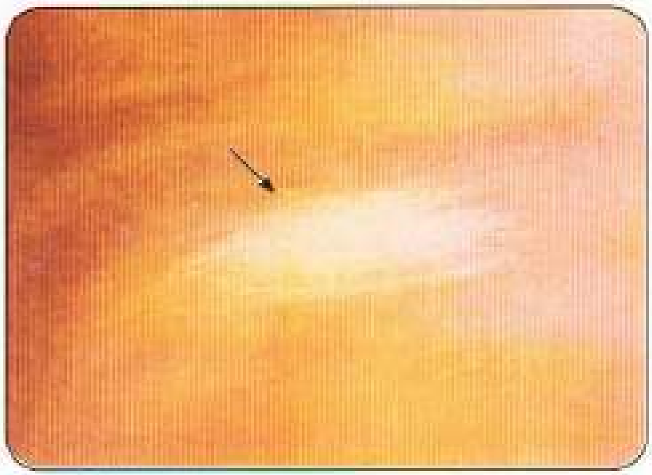


Figure 24.1: Macule.

Papule

- Elevated solid area measuring 5 mm or less

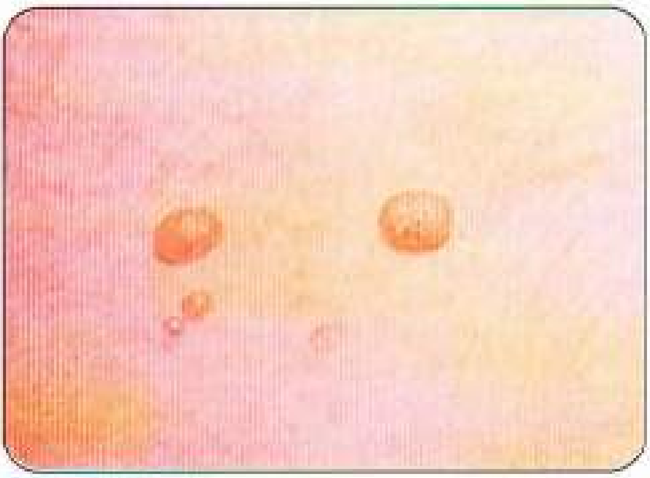


Figure 24.2: Papule.

Vesicle

- Elevated fluid-filled lesion measuring 5 mm or less

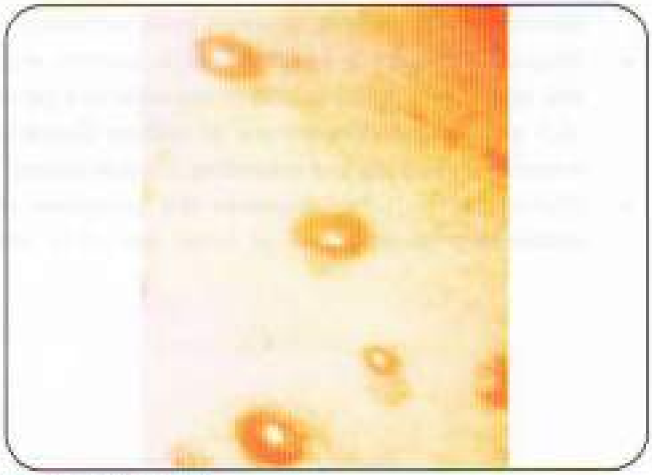


Figure 24.3: Vesicle.

Bulla

- Elevated fluid-filled lesion measuring greater than 5 mm

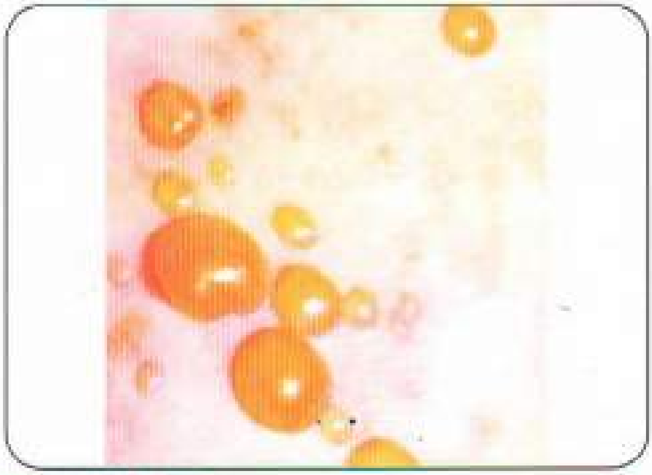


Figure 24.4: Bullae.

Blister

- Common term for vesicle or bulla

Pustule

- Discrete, pus-filled raised area

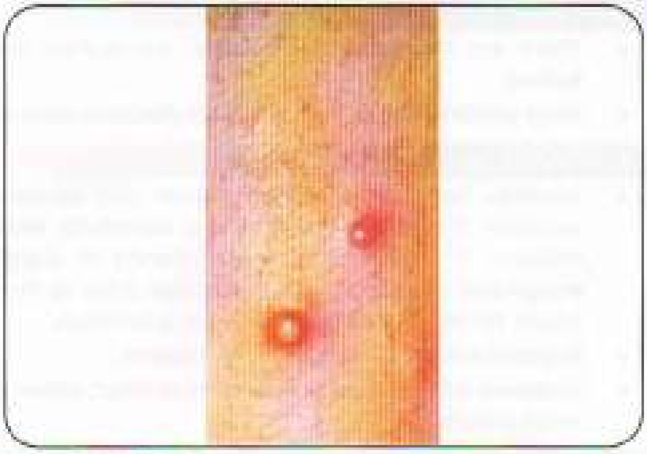


Figure 24.5: Pustule.

Wheals

- These are flat-topped, palpable lesions of variable size, duration, and configuration that represent dermal collection of edema fluid.

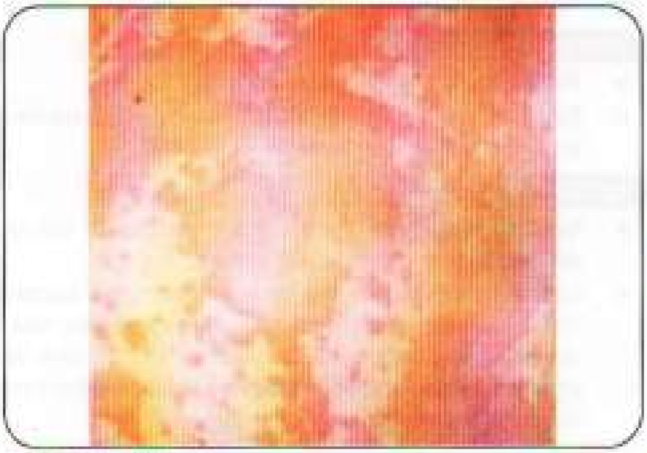


Figure 24.6: Wheals.

Cysts

- These are circumscribed, thick-walled lesions that are located deep in the skin; they are covered by a normal epidermis and contain fluid or semisolid material.

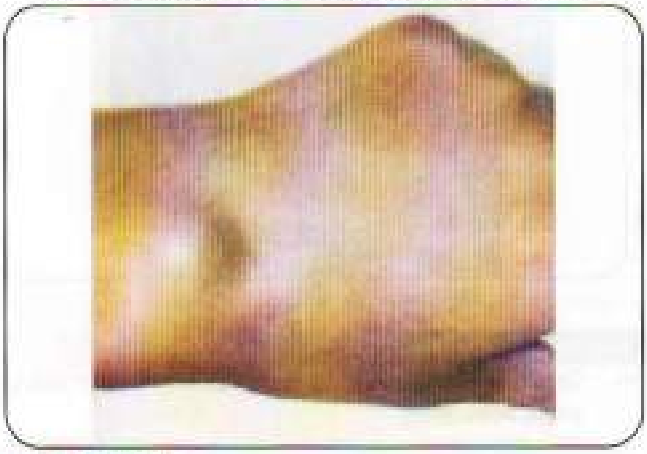


Figure 24.7: Cyst.

EXAMINATION AND ASSESSMENT OF THE SKIN

- The skin is the largest, most accessible and easily examined organ of the body.
- Many skin diseases are easily recognized by simple inspection. For accurate diagnosis, complete history and physical examination are necessary.
- Optimal examination of the skin must be performed in a well-lit room. Entire skin surface must be inspected including hair, nails, scalp, and mucous membranes. In infant examination, great care must be necessary to prevent cooling or embarrassment.
- After assessment the general health of the patient, a detailed history of the skin symptom should be obtained including date of onset, inciting factors, evolution of lesions, and the presence or absence of pruritis. Recent immunizations, infections, and allergies may be directly related to new rashes. The family history may suggest a hereditary or contagious process, and other family members are also examined.
- Then distribution and pattern of the skin lesions are examined. The arrangement of lesions may be distinctive. Grouping of tense vesicles is seen in herpes simplex and zoster, with a characteristic linear arrangement in the latter. Annularity (a tendency to form rings) is typical in erythema multiforme, fixed drug eruption, and fungal infections.

NEONATAL DERMATOLOGY

- The skin of the newborn differs from that of an adult. It is thinner, less hairy, has fewer sweat and sebaceous gland secretions, and has weaker inter-cellular attachments.

Mongolian spots

- These are flat, slate-gray to blue-black, poorly circumscribed macules. Mongolian spots are commonly located over the lumbo-sacral area and buttocks.

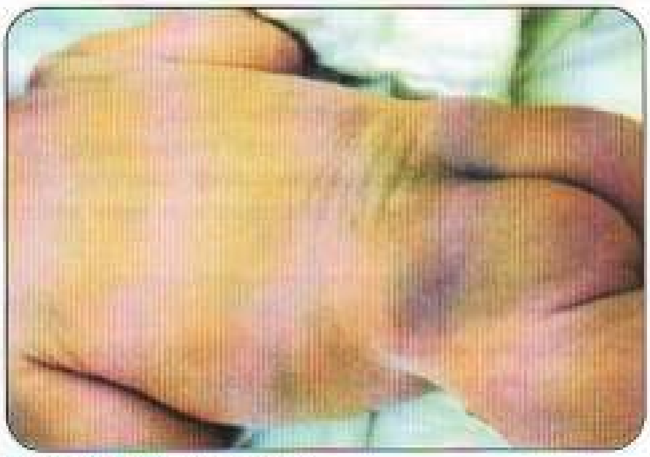


Figure 24.8: Mongolian spots.

- The spots may be 1–10 cm in size and may be single or multiple. There is accumulation of melanocytes deep within the dermis. Mongolian spots usually fade without therapy by age 7.

Erythema toxicum

- This is a benign, self-limited and asymptomatic disorder. It is of unknown etiology. It occurs in up to 50% of term infants. Preterm infants are less commonly affected.
- Lesions usually begin 24–48 hours after birth, but may appear up to the 10th day of life. There is intense erythema with a central papule or pustule. Typically, lesions are 2–3 mm in diameter present on the back, face, chest, and extremities. The palms and soles are usually spared.
- A smear of material from a central pustule shows numerous eosinophils. Eosinophilia may be present in up to 20% of patients.
- The eruption fades spontaneously within 5–7 days and no treatment is needed.

Cutis marmorata

- It is a transient, net-like, reddish-blue mottling of the skin due to variable vascular constriction and dilatation.
- It is a normal response to chilling, and upon re-warming, normal skin color returns.
- In neonates, the condition is benign but if persists beyond 6 months of life, it may be a sign of congenital hypothyroidism.

Milia

- These are yellowish-white, shiny vesicles, pinpoint-sized or larger and usually grouped.
- These are caused by plugging and distention of sebaceous ducts. These are noted during the first or second week of life on the forehead, nose, nasolabial folds, chin and cheeks.

Sclerema

- It is an intense, non-pitting hardening of subcutaneous tissues, usually of the trunk and proximal portions of the extremities. It may accompany septicemia, pneumonia, and severe gastroenteritis.
- Sclerema may begin on buttocks, cheeks, thighs, calves or trunk and becomes generalized. Overlying skin is cold, hard, mottled, reddish-purple or waxy white in color.

BACTERIAL INFECTIONS OF THE SKIN

- Normally, the skin has a variety of bacterial flora, including the major pathogenic varieties of staphylococci and streptococci.
- The degree of their pathogenisity depends on the invasiveness and toxigenicity of the specific organism, the integrity of the skin, the barrier of the host, and the immune and cellular defenses of the host.

IMPETIGO

- There are two types of impetigo: non-bullous and bullous.
- Most predominant organism is Staphylococcus aureus.

Clinical findings

- Impetigo begins as a reddish macule that becomes vesicular. It ruptures easily, leaving superficial, moist erosions. It tends to spread peripherally in sharply marginated irregular outlines. Exudate dries to form heavy, honey-colored crusts. Pruritus is common.
- Regional adenopathy is commonly present.
- Diagnosis is by cultures of fluid from an intact blister or moist plaque.

Complications

- Osteomyelitis
- Septic arthritis
- Pneumonia
- Cellulitis
- Septicemia

Management

- Topical application of bactericidal ointment
- Systemic administration of oral or parenteral antibiotics in severe or extensive lesions

CELLULITIS

- Cellulitis is a spreading bacterial infection of the skin and the tissues immediately beneath the skin.
- Cellulitis may be caused by many different bacteria. The most common are Streptococcuspyogenes and S. aureus. Streptococci spread rapidly in the skin and produce enzymes that inhibit the ability of the tissue to control the infection.

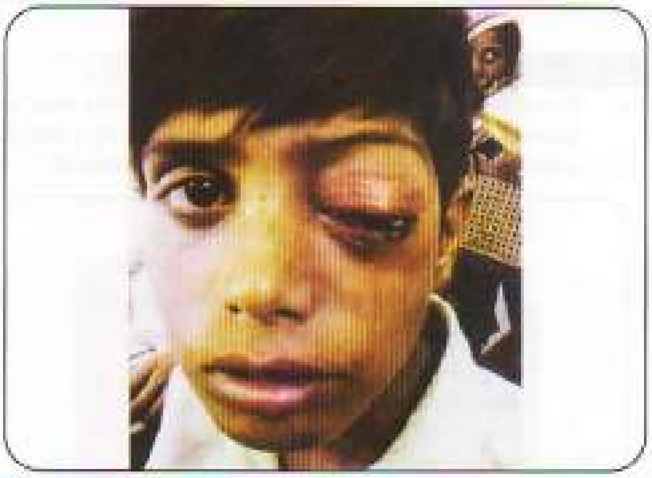


Figure 24.9: Cellulitis around eye.

Clinical findings

- Cellulitis most commonly develops on the legs but can occur anywhere.
- The first symptoms are redness, pain, and tenderness over an area of skin. These symptoms are caused both

by the bacteria themselves and by the body's attempts to control the infection.

- The infected skin becomes hot and slightly swollen. Fluid-filled blisters, which may be small (vesicles) or large (bullae), sometimes appear on the infected skin.
- Erysipelas is one form of streptococcal cellulitis in which the skin is bright red and swollen and the edges of the infected area are raised. The swelling occurs because the infection blocks the lymphatic vessels in the skin.

Complications

- Most people with cellulitis feel only mildly ill, but some may have a fever and chills. As the infection spreads, nearby lymph nodes may become enlarged and tender (lymphadenitis). Other complications are lymphangitis, skin abscesses, and spread through the blood (sepsis).

Diagnosis and management

- Diagnosis is mainly clinical but culture of bacteria from blood, pus, or tissue specimens usually is required if a person is seriously ill.
- Antibiotics, such as cephalexin, that are effective against both streptococci and staphylococci are used. People with rapidly spreading cellulitis, high fever, or other evidence of serious infection should receive intravenous antibiotics.
- Antibiotics are continued for 10 days or longer even though the symptoms may disappear earlier.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

- *This is an acute, widespread erythema and epidermal peeling caused by staphylococcal exotoxin.*
- Staphylococcal Scalded Skin Syndrome (SSSS) almost always occurs in infants, children <6 years old, and immuno-suppressed children.
- Epidemics may occur in nurseries, transmitted by the hands of personnel in contact with an infected infant. However, nursery personnel may be nasal carriers of *S. aureus*. Sporadic cases also occur.

Etiology

- Group-II coagulase–positive staphylococci are responsible.
- They secrete exfoliatin (also called epidermolysin), an epidermolytic toxin that splits off the upper part of the epidermis just beneath the granular cell layer. The inciting infection may be on the skin but usually is in the eye or nasopharynx. The toxin enters the circulation and affects the skin systemically, as in scarlet fever.

Clinical findings

- In infants, illness often begins during the first few days of life with a localized crusted infection (often impetigo-like), most often at the umbilical stump or in the diaper area.
- Sporadic cases often start with a superficial crusted lesion, frequently around the nose or ear.
- Within 24 h, tender areas appear around the crusted area and may become painful and generalized. Large blisters arise on the erythematous skin and quickly break to produce erosions. The epidermis peels off easily, often in large sheets, when the red areas are rubbed (Nikolsky's sign). Widespread desquamation of the skin occurs within 36 to 72 h, and patients may become very ill with systemic manifestations (e.g. malaise, chills, fever).
- Loss of the protective skin barrier can lead to sepsis and to fluid and electrolyte imbalance.

Diagnosis

- Symptoms and signs are indistinguishable clinically from Toxic Epidermal Necrolysis (TEN).
- Cultures should be obtained from the skin and nasopharynx.
- Diagnosis is confirmed by skin biopsy and examination of frozen tissue sections or exfoliative cytology.
- Differential diagnosis includes drug hypersensitivity (most notably, TEN), viral exanthemas, and scarlet fever, but none of these causes a painful rash. Bullae, erosions, and an easily loosened epidermis occur in thermal burns, genetic bullous diseases (e.g. some types of epidermolysisbullosa), and acquired bullous diseases (e.g. pemphigus vulgaris, bullous pemphigoid).

Management

- With proper diagnosis and therapy, death rarely occurs.
- Systemic penicillinase-resistant anti-staphylococcal antibiotics (e.g. cloxacillin, dicloxacillin, cephalexin) must be started as soon as the clinical diagnosis is made, without waiting for culture results.
- Corticosteroids are contraindicated, and topical therapy and patient handling must be minimized.
- If the disease is widespread and the lesions are weeping, the skin should be treated as if it were burned. Hydrolyzed polymer gel dressings may be very useful, and the number of dressing changes should be minimized.
- Because the split is high in the epidermis, the stratum corneum is quickly replaced and healing is usually within 5 to 7 days after the start of treatment.

ERYSIPELAS

- A superficial cellulitis with marked lymphatic vessel involvement caused by group A beta-hemolytic streptococci.

Clinical findings

- The lesion is well demarcated, shiny, red, edematous, indurated, and tender; vesicles and bullae sometimes develop.

- The face (often bilaterally), arms, and legs are the most common sites. Patches of peripheral redness and regional lymphadenopathy occasionally occur.
- High fever, chills, and malaise are common. Erysipelas may be recurrent and may result in chronic lymphedema.

Management

- Penicillin V or erythromycin should be given for 2 weeks. In acute cases, penicillin G IV every 6 h gives a rapid response and should be replaced by oral therapy after 36 to 48 h. In cases resistant to these antibiotics, cloxacillin or cephalexin has been used.

VIRAL INFECTIONS OF THE SKIN

- Viruses are intracellular parasites that produce their effect by using the intracellular substances of the host cells.
- After a virus penetrates a cell of the host organism, it sheds the outer shell and disappears within the cell, where the nucleic acid core stimulates the host cell to form more virus material from its intracellular substance.

MOLLUSCUM CONTAGIOSUM

- A poxvirus infection characterized by skin-colored, smooth, waxy, umbilicated papules 2 to 10 mm in diameter.
- Transmission, often venereal, is by direct contact. Numerous small papules may appear anywhere on the skin, often in the genital and pubic area. The lesions are usually asymptomatic, unless secondarily infected, and may be discovered when the patient is examined for a sexually transmitted disease.
- Lesions can be diagnosed easily by the characteristic central umbilication.
- Successful treatment usually requires destroying each lesion by freezing; by removing the central core of the papule with a needle, a comedo extractor, or the tip of a #11 scalpel blade; or by trichloracetic acid application (25 to 40% solution).

HERPES SIMPLEX

- An infection with herpes simplex virus characterized by one or many clusters of small vesicles filled with clear fluid on slightly raised inflammatory bases.

Etiology

- The two types of Herpes Simplex Virus (HSV) are HSV-1 and HSV-2.
- HSV-1 commonly causes herpes labialis, herpetic stomatitis, and keratitis.
- HSV-2 usually causes genital herpes, is transmitted primarily by direct (usually sexual) contact with lesions, and results in skin lesions.
- After initial eruption, HSV remains dormant in the nerve ganglia. Recurrent herpetic eruptions can occur, precipitated by overexposure to sunlight, febrile illnesses, physical or emotional stress, or immunosuppression.

Clinical findings

- The lesions may appear anywhere on the skin or mucosa but are most frequent around the mouth, on the lips on the conjunctiva and cornea, and on the genitalia.
- After a prodromal period (generally <6 h in recurrent HSV-1) of tingling discomfort or itching, small tense vesicles appear on an erythematous base. Single clusters vary in size from 0.5 to 1.5 cm, but groups may coalesce.
- Skin lesions involving the nose, ears, or fingers may be particularly painful. The vesicles persist for a few days, and then begin to dry, forming a thin yellowish crust.
- Healing generally occurs in 8 to 12 days after onset. Individual herpetic lesions usually heal completely, but recurrent lesions at the same site may cause atrophy and scarring.
- **Primary infection of HSV-1** typically causes a gingivostomatitis, which is most common in infants and young children. Symptoms include irritability, anorexia, fever, gingival inflammation, and painful ulcers of the mouth.
- **Primary infection of HSV-2** typically occurs on the vulva and vagina or penis in young adults. Illness is accompanied by fever, malaise, and tender inguinal adenopathy. HSV-2 infection may occur in newborns and cause severe disseminated disease.
- HSV outbreaks may be followed by typical erythema multiforme. Eczema herpeticum is a complication of HSV infection in which patients have severe disease in skin regions with eczema.

Diagnosis

- Diagnosis is confirmed by cultures for the virus, seroconversion and a progressive increase in serum antibodies to the appropriate serotype (in primary infections), and biopsy findings.
- A Tzanck preparation of the base of a lesion often reveals multinucleate giant cells in HSV or varicella-zoster virus infection. Newer techniques such as the polymerase chain reaction of CSF may allow early noninvasive diagnosis of herpes simplex encephalitis.
- HSV should be distinguished from herpes zoster, which rarely recurs and usually causes more severe pain and larger groups of lesions distributed along a dermatome.

Management

- Systemic treatment with acyclovir is used in serious herpes infections, such as disseminated neonatal disease, in herpes simplex encephalitis, and in immunocompromised patients. Acyclovir, valacyclovir, and famciclovir can each be used for suppression of recurrent eruptions. Topical acyclovir can be used.

- Secondary infections are treated with topical antibiotics (e.g. neomycin-bacitracin ointment) or, if severe, with systemic antibiotics.

FUNGAL INFECTIONS OF SKIN

- Fungal infections are caused by a group of closely related filamentous fungi that invade primarily the stratum corneum, hair, and nails.
- Fungal skin infections are most often transmitted from one person to another or from infected animals to humans. Atopic individuals are more susceptible to fungal skin infections. Fungi exert their effect by means of an enzyme that digests and hydrolyzes the keratin of hair, nails, and the stratum corneum. Dissolved hair breaks off to produce the bald spots characteristic of tineacapitis.

TINEA CORPORIS (Ringworm)

- *Trichophytonsp* is usually the cause.
- It is a superficial fungal infection of the non-hairy skin.
- It is labeled as ringworm because of its characteristic configuration consisting of pruritic, annular lesions with central clearing, and an active vesicular border made up of microvsicles which rupture and then scale.
- Lesions may be single or multiple and begin as red papules or pustules which rupture and form papulosqamous lesions. Lesions spread out from the periphery and begin to clear centrally. After several weeks, patches may expand up to 5 cm in diameter.
- The diagnosis of tinea is confirmed by KOH examination of the skin.
- Tinea infections respond rapidly to topical antifungal creams (miconazole, clotrimazole, ketoconazole). When lesions are multiple and widespread, oral therapy with griseofulvin is indicated.

DIAPER DERMATITIS

- Because the diaper area is warm, often moist, and frequently contaminated by feces, which are full of micro-organisms, diaper dermatitis is one of the most common skin disorders of infancy.

Irritant diaper dermatitis

- Diaper dermatitis can be regarded as the prototype of irritant contact dermatitis.
- As a reaction to over-hydration of the skin, friction, maceration and prolonged contact with urine and feces, retained diaper soaps and topical preparations, the skin of the diaper area becomes erythematous and scaly often with papulovesicular or bullous lesions, fissures and erosions.
- The eruption can be patchy or confluent but inguinal folds are often spared.
- Secondary infection with bacteria and yeast is common.
- Candidial infection can be identified by red-pink tender skin that has numerous 1–2 mm pustules and papules at the periphery of dermatitis called satellite lesions.
- Dermatitis can be cleared by:
  1. Frequent diaper change
  2. Gentle, thorough cleansing of the area
  3. Application of lubricants and barrier pastes

Candidal dermatitis

- It appears as a bright red eruption, with sharp borders and pinpoint satellite papules and pustules.
- Candidal diaper dermatitis is occasionally associated with oral thrush. It is a common sequel of oral or parenteral antibiotic therapy.
- Candidal diaper dermatitis is suspected whenever intertriginous areas are involved or a diaper rash fails to respond to symptomatic treatment.
- Most cases are well treated with topical anti-fungal therapy.

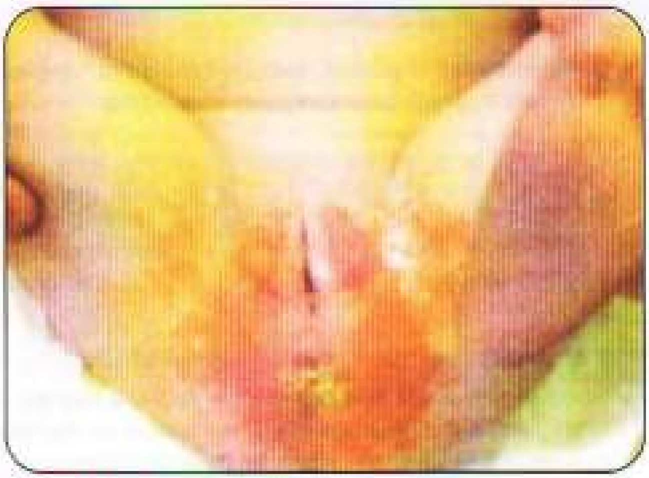


Figure 24.10: Diaper dermatitis.

Staphylococcal diaper dermatitis

- Irritant diaper dermatitis is frequently complicated by secondary staphylococcal infection.
- There are thin walled pustules on an erythematous base (larger than those seen with candida). Typically, these rupture rapidly and dry, producing scaling around red base.
- Gram stain of pustule contents demonstrates neutrophils and clusters of gram-positive cocci.
- Rapid resolution is with topical antibiotics.

ATOPIC DERMATITIS

CASE

A 4-year-old boy has ***dry, scaly rash*** in his antecubital and popliteal fossa. There are ***areas of lichenification***. His rash becomes worse in the winter months.

- Chronic, pruritic, superficial inflammation of the skin, frequently associated with a personal or family history of allergic disorders (e.g. hay fever, asthma).

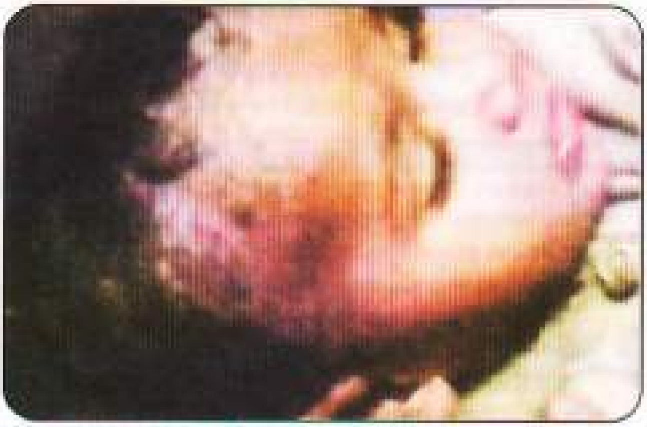


Figure 24.11: Atopic dermatitis.

Etiology

- Susceptibility is genetic, but the disorder is triggered by various environmental agents and factors.
- Patients with atopic dermatitis usually have high serum levels of reaginic (IgE) antibodies, peripheral eosinophilia, and high levels of cAMPphosphodiesterase in their WBCs, but the etiologic significance of these findings is unknown.

Clinical findings

- Atopic dermatitis may begin in the first few months of life, with red, weeping, and crusted lesions on the face, scalp, diaper area, and extremities.
- In older children or adults, it may be more localized and chronic, typically appearing as erythema and lichenification in the antecubital and popliteal fossae and on the eyelids, neck, and wrists.
- The course is unpredictable. Although the dermatitis often improves by age 3 or 4 yr, exacerbations are common during childhood. Wool garments commonly cause exacerbations.

Complications

- Patients with long-standing atopic dermatitis may develop cataracts while in their 20s or 30s. Cataracts may be a feature of atopy or may result from extensive systemic and topical corticosteroid use.
- Herpes simplex may induce a generalized painful vesicular eruption and sometimes a grave febrile illness (eczema herpeticum) in atopic patients.
- House dust mites in bedding, upholstered furniture, and carpeting may significantly exacerbate atopic dermatitis.

Diagnosis

- Diagnosis is based on:
    - Distribution and duration of lesions.
    - A family history of atopic disorders.
    - Presence of lichenification.

Management

- Precipitating agents should be avoided if possible.
- Corticosteroid creams or ointments applied three times daily are most effective. Supplemental use of white petroleum, hydrogenated vegetable oil (as for cooking), or hydrophilic petroleum (unless the patient is allergic to lanolin) may be advisable. These emollients also help hydrate the skin, which is important. Prolonged, widespread use of high-potency corticosteroid creams or ointments should be avoided in infants because adrenal suppression may ensue.
- Bathing should be minimized and oils, corticosteroids or emollient ointments should be applied within 3 minutes of bathing, before the skin is dried, to enhance effectiveness.
- Oral corticosteroids should be considered in resistant cases but, if given, are best used in 1–2 week courses.

PARASITIC SKIN INFECTIONS

PEDICULOSIS

- It is an infestation by lice.
- Pediculosis may involve the head (by *Pediculushumanuscapitis*), the body (*P. humanuscorporis*), or the genital area (*Phthirus pubis*).
- Infestation is widespread in facilities that are overcrowded with poor personal hygiene and unclean clothing.

Clinical findings

- **P. humanuscapitis** is transmitted by personal contact and is common among school children.
- Pruritus is severe, and excoriation of the scalp, sometimes with secondary bacterial infection, may occur.
- Moderate discrete posterior cervical adenopathy is frequent. Small, ovoid, grayish white nits (ova) are seen fixed to the hair shafts, sometimes in great

numbers. Unlike scales, they cannot be dislodged; they mature into lice in 3 to 14 days.

- **P. humanuscorporis** is uncommon with good hygiene.

Prevention and management

- Prevention of pediculosis and reinfestation includes teaching children and others to practice good hygiene and to avoid sharing combs, brushes, caps, scarves, and clothing.
- As with scabies, the patient's family members and close social contacts should be treated.
- Permethrin cream 5% is currently the treatment of choice. Its safety has been shown in the treatment of scabies. For pediculosis, it should be left in place for 6 to 12 hours before being washed off. Nits and lice can be mechanically removed with a comb in most cases. Resistance to permethrin is increasing.

SCABIES

CASE

A 3-year-old child presents with a 2 week history of a ***rash*** limited to the feet and ankles. The papular rash is both ***pruritic*** and ***erythematous***. Lesions seem to spare the face. There are areas of lichenification from repeated scratching. There are some lesions in the webbing of her hands. ***Other family members*** are also ***affected***.

- *A transmissible ectoparasite infection, characterized by superficial burrows, intense pruritus, and secondary infection.*

Etiology

- Scabies is caused by the mite *Sarcoptesscabiei*. The impregnated female mite tunnels into the stratum corneum and deposits her eggs along the burrow. The larvae hatch within a few days.
- Scabies is transmitted readily by skin-to-skin contact with an infected person.

Clinical findings

- A delayed hypersensitivity reaction (an intensely itching papular eruption) is characteristic; beginning 30 to 40 days after the infestation is acquired.
- Pruritus is most intense when the patient is in bed.
- Patient may have hundreds of itching papules. The burrow is a fine, wavy, and slightly scaly line a few millimeters to 1 cm long. A tiny mite (0.3 to 0.4 mm) is often visible at one end of the burrow. Burrows occur predominantly on the finger webs, wrists, arms, legs, and axillary folds.
- Diagnosis requires demonstration of a burrow. Diagnosis should be confirmed by microscopy of scrapings from its surface. The scrapings should be placed on a slide with glycerol, mineral oil, or immersion oil and covered with a cover slip. Finding the mite, ova, or fecal pellets clinches the diagnosis.

Management

- Treatment with topical medications (scabicide) is usually effective, and the medication must be applied thoroughly to all skin from the neck down, particularly the finger webs, genitalia, perianal areas, and toe webs. Medication should remain on the skin for 12 hours, preferably 24 hours, and washed off.
- The topical medication of choice is permethrin cream 5% because it is safe for all age groups.
- Lindane cream or lotion is also used.
- All skin-to-skin contacts (e.g. social contacts, all family members) should be treated at the same time.
- Concomitant bacterial infections may require systemic antibiotics but often clear spontaneously when scabies is cured

ERYTHEMA MULTIFORME

- EM is a reactive syndrome characterized by "target" lesions of the skin and mucous membranes most commonly precipitated by an infection (usually HSV).

Classification

- **EM Minor:** Mild, sudden onset of papules, some of which evolve into target lesions. No prodrome or mucosal involvement. Recurrences common.
- **EM Major:** EM associated with mucosal lesions and systemic symptoms.

Clinical findings

- Skin lesions appear abruptly 3 to 14 days after precipitant (herpes labialis in 50%) and new lesions can continue to appear for up to 10 days.

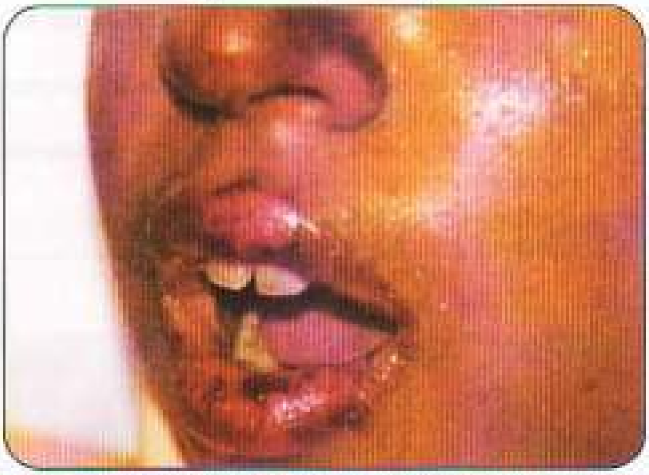


Figure 24.12: Typical lesions on tongue in erythema multiforme.

- Fever, malaise, and mucous membrane involvement may also be present.
- Skin lesions are typical 1–3 cm target or iris lesions. Oral, ocular and genital mucous membranes are involved.

Differential diagnosis

- Viral exanthems
- Bullous diseases
- Urticaria
- Secondary syphilis
- Psoriasis
- Drug reaction

Management

- For EM management, if a precipitant can be identified, it should be treated or removed.
- In recurrent EM cases secondary to HSV, daily prophylactic acyclovir may be necessary.
- In most cases of EM, the rash will self-resolve in 5 to 15 days without treatment.
- Symptomatic relief for pruritic skin lesions can be obtained with systemic antihistamines (diphenhydramine, cetirizine HCl), emollients (hydrated petrolatum, Vaseline, moisturizers), and topical steroids.
- In severe EM, systemic steroids (prednisone, methylprednisolone) can be added.
- Open skin lesions can be treated with topical antibiotics.
- Oral lesions can benefit from anesthetic rinses.
- Ocular lesions need topical treatment advised by an ophthalmologist.
- In severe refractory or recurrent EM cases, azathioprine, thalidomide, dapsone, or cyclosporine may give benefit.

Course and prognosis

- EM appears abruptly 3 to 14 days after insult (HSV, infection, drug, etc.).
- Skin lesions fully evolve in 72 hours and persist for a week.
- Lesions can be pruritic or painful, systemic symptoms and mucosal involvement may be present.
- EM typically resolves after 2 weeks with no sequelae, but recurrences are common.

STEVENS-JOHNSON SYNDROME (SJS)

CASE

A 2-year-old child with a ***rash*** which developed when he ***took a medicine*** for fever 3 days ago. On examination, there are raised erythematous non-purpuric patches with central white and bluish discoloration on the limbs with a few small vesicular lesions on the calves. There is marked ***conjunctivitis*** with photophobia and the ***lips*** are ***cracked*** and ***weeping.***

- SJS is a rare, severe cutaneous drug reaction characterized by tenderness of the skin/mucosa, followed by extensive exfoliation that is potentially life-threatening.

Pathophysiology

- Pathogenesis is because of a host's impaired capacity to metabolize reactive drug metabolites. The metabolites then trigger extensive keratinocyte death (apoptosis), loss of cohesion, necrosis resulting in full-thickness epidermal necrolysis.
- Drugs implicated include NSAIDs (phenylbutazone, piroxicam), antibiotics (amithiozone, aminopenicillins) sulfa drugs (sulfadoxine, sulfadiazine, sulfasalazine, trimethoprim-sulfa-methoxazole), allopurinol, antiretrovirals, and antiepileptics (barbiturates, carbamazepine, phenytoin, and lamotrigine).

Clinical findings

- One to three weeks after drug exposure, SJS begins with fever, pain with swallowing and stinging eyes.
- Up to 3 days later, the skin lesions appear on the trunk spreading to the upper extremities and face. Skin turns dusky red before dermal–epidermal detachment with sheets of skin falling off leaving raw, red denuded area.
- The skin lesions are typically more widespread than in EM and are accompanied by involvement of **two or more mucosal surfaces** (eyes, oral cavity, upper airway or esophagus, gastrointestinal tract, or ano-genital mucosa).
- Systemic symptoms include fever, malaise, myalgia, arthralgias, nausea and vomiting, diarrhea, and conjunctival burning. Pain from mucosal ulceration is often severe.
- Corneal ulceration, anterior uveitis, panophthalmitis, bronchitis, pneumonitis, myocarditis, hepatitis, enterocolitis, polyarthritis, hematuria, and acute tubular necrosis leading to renal failure may occur.
- Nikolsky sign: Lateral mechanical pressure causes epidermal detachment.
- There are erosions on buccal, ocular, genital mucosae; conjunctivalhyperemia, and keratitis.

Differential diagnosis

- Erythema multiforme
- Staphylococcal Scalded Skin Syndrome (SSSS)
- Urticaria
- Kawasaki's disease
- Thermal burns
- Phototoxic eruptions
- Generalized fixed drug eruption
- Generalized erythroderma (from severe psoriasis, atopic dermatitis, mycosis fungiodes, etc.)
- Systemic lupus erythematosus

Management

- SJS management consists rapid diagnosis and of **elimination of the causative agent**.
- Patient best cared for in a burn or intensive care unit with IV fluid and electrolyte replenishment, temperature control, and vigilant wound care.

- Careful daily wound care with minimal manipulation can lead to regrowth of epidermis in 1 to 3 weeks.
- Patient needs nutritional support, sheepskin or air-fluid bedding, daily saline or Burrow solution compresses, paraffin gauze or colloidal gel (Hydrogel) dressing of denuded areas, saline compresses on the eyelids, lips, or nose, analgesics and urinary catheterization if needed. And a daily examination for infection and ocular lesions.
- Ocular lesions need topical treatment advised by an ophthalmologist. Ocular sequelae such as corneal scarring can lead to vision loss. Application of cryopreserved amniotic membrane to the ocular surface during the acute phase of the disease limits the destructive and long-term sequelae. Early topical steroid treatment may also reduce ocular sequelae.
- Oral lesions should be managed with mouthwashes and glycerine swabs.
- Vaginal lesions should be observed closely and treated to prevent vaginal stricture or fusion.
- Topical anesthetics (diphenhydramine, lidocaine) may provide relief from pain.
- Pressure points and perioral areas heal more slowly.
- Antibiotic therapy is appropriate for documented secondary bacterial infection. Systemic antibiotics are indicated for documented urinary or cutaneous infections and for suspected bacteremia (*Staphylococcus aureus or Pseudomonas aeruginosa*) because infection is the leading cause of death.
- The use of systemic steroids for SJS management is controversial.
- High-dose IV immunoglobulins may be of some benefit if administered early. IV immunoglobulin (IVIG; 1.5–2.0 g/kg/day × 3 days) should be considered.

Course and prognosis

- Course is similar to that of severe widespread thermal burns.
- New lesions occur in crops, and complete healing may take 4–6 weeks; ocular scarring, visual impairment, and strictures of the esophagus, bronchi, vagina, urethra, or anus may remain.
- Outcome is worse for in children who are older, or have more extensive skin involvement.
- Mortality rate is 5%.

Prevention

- Those who do recover from SJS need to be aware of their drug sensitivity and possible cross-reactants.
- Re-exposure to the offending agent can lead to a faster, more severe SJS episode, thus drugs should not be re-administered.

CHAPTER 25

Pediatrics Surgery

CLEFT LIP/CLEFT PALATE

- Cleft of the lip is due to hypoplasia of the mesenchymal layer, resulting in a failure of the medial nasal and maxillary processes to join.
- Cleft of the palate is due to failure of the palate shelves to approximate or fuse.

Incidence

- Cleft lip with or without cleft palate is about 1:750 births.
- Isolated cleft palate is seen in 1:2500 births.
- Cleft lip with or without cleft palate is twice as common in boys.
- Isolated cleft palate is seen more frequently in girls.

Etiology

- Possible etiologies are maternal drug exposure, syndrome-malformation complex, isolated-unknown, or genetic.
- Genetic factors are more important in cleft lip with or without cleft palate than in cleft palate alone.
- Both may occur sporadically.
- Incidence of associated congenital malformations and of impairment in development is increased in children with cleft defects, especially in those with cleft palate alone.

Clinical findings

- Cleft lip may vary from a small notch to a complete separation extending into the floor of the nose.
- Cleft may be unilateral (more often on the left side) or bilateral. Deformed, supernumerary, or absent teeth are associated.
- Isolated cleft palate occurs in the midline and may involve only the uvula or may extend into or through the soft and hard palates to the incisive foramen.

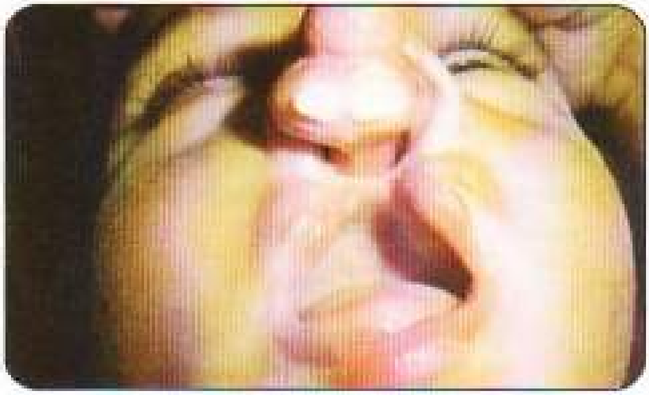


Figure 25.1: Cleft lip.

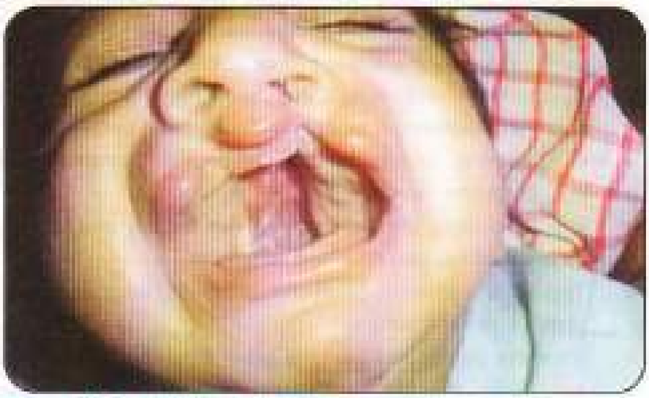


Figure 25.2: Cleft lip and palate.

Recurrences

- The recurrence risk for unilateral cleft lip and palate is 4% for a couple with one affected child and increase to 9% with two affected children.

Complications

- Feeding difficulties
- Recurrent serous otitis media
- Hearing and language delayst
- Speech problems, hypernasality, articulation errorst
- Dental and orthodontic complicationst
- Cosmetic appearance, psychological problemt

Pierre robin sequence

- A form of cleft palate associated with micrognathia (hypoplastic mandible) and projection of tongue posteriorly during development, preventing closure of the palate, is called Pierre Robin sequence.

Associated anomalies

- Abnormalities of the cardiovascular, renal, central nervous and gastrointestinal systems are found, particularly when part of a chromosomal syndrome.

Management

- Feeding by using a soft and long teat with an enlarged hole, tube feeding in erect position, or breastfeeding in prone position.
- Hearing screening test of a new born should be done.
- Audiometry should be done after that
- The usual practice is to repair the cleft lip at 3 months of age and the palate at 6 months or later. Too early a repair may interfere with mid-facial growth.
- Speech therapy is important.

ESOPHAGEAL ATRESIA AND TRACHEO-ESOPHAGEAL FISTULA

CASE

An infant develops ***drooling shortly after birth***. When he is given her first feeding, it comes out of his mouth, and he ***coughs*** and ***chokes***. During the resuscitation, ***placement of an orogastric tube meets resistance***.

- There is discontinuity of esophageal lumen with or without communication with trachea.
- It is characterized by a blind esophageal pouch and a fistulous connection between the proximal or distal esophagus (or both) and the airway.
- In about 85% of the affected infants, the fistula is between the distal esophagus and the airway.
- There may be history of polyhydramnios as there is a high level of GIT obstruction.
- It has an association with VATER and VACTERAL syndrome (Vertebral, Anorectal, Cardiac, Tracheo-esophageal, renal, and Limb anomalies).

Types

There are five types:

1. Esophageal atresia with no tracheal communication
2. Esophageal atresia with fistula from upper pouch
3. Upper blind esophageal pouch and lower pouch communicating with trachea
4. Both the pouches of esophagus communicating with trachea
5. No esophageal atresia but fistulous communication with trachea present (H-type fistula)

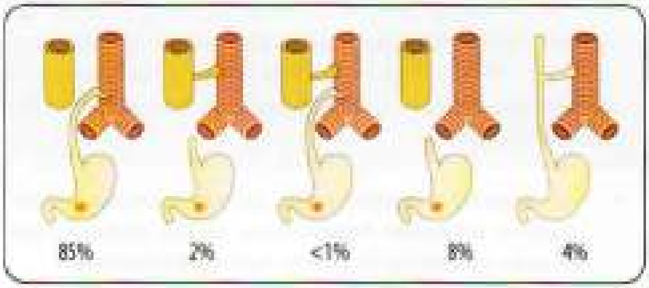


Figure 25.3: Illustration of trachea-esophageal fistula

Clinical findings

- Infant presents in the first hours of life.
- There are copious secretions (bubbly baby syndrome), choking, cyanosis, and respiratory distress.
- On chest X-ray, after careful placement of a nasogastric tube to the point at which resistance is met, the tube will be seen in the blind pouch. If the tracheoesophageal fistula is present to the distal esophagus, gas will be present in the intestine. There will be no gas in the intestine in a case of esophageal atresia without tracheoesophageal fistula.

Management

- Feeding is stopped immediately and IV fluids are given.
- NG tube in the proximal pouch should be placed for continuous suction to drain secretions and prevent aspiration.
- Head of the bed should be elevated to prevent reflux of gastric contents through the distal fistula into the lungs.
- Definitive treatment is by operation. It depends on the distance between the segments of the esophagus.

Prognosis

- Prognosis depends on the presence or absence of associated anomalies.

CONGENITAL DIAPHRAGMATIC HERNIA

CASE

A newborn infant develops cyanosis and ***respiratory distress immediately after birth***. Abdomen is flat (***scaphoid***). ***No breath sounds are heard on the left side of his chest***, but they are audible on the right. Heart sounds are heard on the right side of the chest. Chest radiograph shows a ***multicystic mass in the left chest*** with a shift of the mediastinum to the right.

- This is the herniation of the abdominal contents into the thoracic cavity.
- Congenital diaphragmatic hernia represents failure of division of the thoracic and abdominal cavities at the 8^{th}–10^{th} weeks of fetal life.
- 30% of infants with diaphragmatic hernia die. Main cause of death is pulmonary insufficiency. There is pulmonary hypoplasia on the affected side. On the affected side, lung has decreased generations of the airways and pulmonary arteries. There may be pulmonary hypertension.
- In a case of diaphragmatic hernia, both lungs are small but the lung on the side of the defect is more severely affected. Pulmonary abnormalities are due to compression by the intra-thoracic abdominal viscera.

Incidence

- 1 in 5,000 live births
- 1 in 2,000 if stillbirths are also included

Site

- 80% of congenital diaphragmatic hernia occurs on the left side (Bochdalek type).
- In 5% of the cases defects are bilateral.

Types

1. **Bochdalek type:** It is the most common type. Herniation is through postero-lateral defect (foramen of Bochdalek).
2. **Morgagni type:** Herniation is through a defect in the anterior diaphragm (foramen of Morgagni).

Clinical findings

- Mild to severe respiratory distress is usually present at birth.
- Mild cases may present beyond the neonatal period.
- As there is displacement of the viscera, abdomen may be scaphoid in shape.
- In the affected hemithorax, breath sounds are absent.
- There is displacement of apex beat to the opposite side.
- There may be vomiting as a result of intestinal obstruction or respiratory distress.

Complications and associated anomalies

- Pulmonary hypoplasia
- Mediastinal shift with vascular kinking
- Pulmonary infection
- Prematurity
- Cardiac anomalies
- Intestinal malformation
- CNS lesions
- Esophageal atresia
- Omphalocele
- Recognized syndromes (Trisomy 21, 13, 18, etc.)

Diagnosis

Antenatal diagnosis

- Main features on maternal ultrasonography are:
    - Polyhydramnios
    - Mediastinal displacement
    - Absence of intraabdominal stomach bubble

X-ray

- Chest X-ray is usually diagnostic.
- X-ray of the chest and abdomen in upright position will show the presence of intestines in the chest and shift of mediastinum.

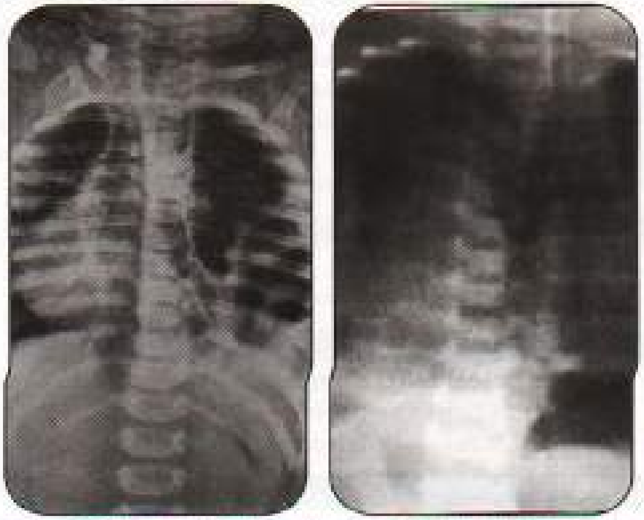


Figure 25.4: Chest X-ray Showing right & Left Diaphragmatic hernia.

- Lateral view may show the intestine passing through the posterior portion of the diaphragm.
- Diaphragmatic hernia is diagnosed by contrast study.
- On X-ray of abdomen and chest, nasogastric (N/G) tube lies in the chest.
- In other conditions, it lies in the abdomen.

Differential diagnosis

- Staphylococcal pneumonia with cysts
- Pneumothorax
- Cystic adenomatoid malformation of the lung

Management

- Extra-Corporeal Membrane Oxygenation (ECMO) has a role in pulmonary hypertension.
- Immediate nasogastric suction produces a reduction of the volume of the herniated intestine.
- Baby should be nursed in head up supine position.
- Abdominal surgical approach is a favored method of repair.

Prognosis

- It depends on the location of the defect and associated anomalies.
- Factors associated with a poor prognosis are:
    - Associated major anomaly
    - Symptoms before 24 hours of age
    - Distress severe enough to require ECMO

CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

CASE

A 4-week-old boy presents with a 10-day history of ***frequent projectile vomiting***. The vomitus is ***non-bilious***. The child feeds vigorously and looks well, but he has been losing weight. After a test feed, there are ***visible left-to-right peristalsis*** and a***olive-shaped mass*** in the midline. Laboratory tests show a ***hypochloremic metabolic alkalosis***. The ***ultrasound*** demonstrates the ***thickened pylorus***.

- In congenital hypertrophic pyloric stenosis, there is marked postnatal hypertrophy of the circular muscle of pylorus leading to gastric outlet obstruction.

Incidence

- The incidence is 1–8:1000 births, with a male predominance.
- In 13% of cases, there is positive family history.
- *There is an increased incidence of pyloric stenosis in* infants with blood groups B and O.

Clinical findings

- There is projectile non-bilious vomiting after every feeding containing only milk.
- Vomiting may be intermittent.
- Vomiting usually starts at 2–4 weeks of age.
- In about 10% of the cases, it starts at birth.
- In premature infants, onset of symptoms may be delayed.

- Infant is hungry and even immediately after vomiting, baby will accept feeds eagerly.
- There is constipation, dehydration, weight loss, and apathy.
- After feeding, the upper abdomen may be distended. There are prominent gastric peristaltic movements from left to right.
- On deep palpation from the left side, in the right upper abdomen, an olive-sized mass (2–3 cm in size) can be felt. This mass is more prominent especially after the child has vomited because the abdominal musculature is more relaxed after vomiting. Mass is located above and to the right of the umbilicus in the mid-epigastrium below the liver edge.
- There may be hematemesis from gastritis caused by repeated vomiting.
- Pyloric stenosis may be associated with other congenital anomalies e.g. tracheo-esophageal fistula.

Diagnosis

- There is delay in gastric emptying (large gastric residue) and an elongated narrowed pyloric channel on upper GIT barium study. On barium study, a bulge of pyloric muscle into the antrum is called shoulder sign. Parallel streaks of barium seen in the narrowed channel produce a double tract sign.
- Ultrasonography (sensitivity 90%) shows a hypoechoic ring with a hyperdensecenter. Circular muscle thickness is greater than 4 mm in pyloric stenosis. There is an overall pyloric length greater than 14 mm.
- There is hypochloremichypokalemic metabolic alkalosis. Serum potassium levels are usually normal, but there may be a total body potassium deficit.
- There is hemoconcentration (raised hemoglobin and hematocrit levels).
- In about 2–5% of the cases, there is unconjugated hyperbilirubinemia. It is associated with decreased level of glucuronyltransferase. It resolves after relief of the obstruction.

Differential diagnosis

- Esophageal stenosis or achalasia:
    - There are no gastric contents in the vomitus. There is no metabolic alkalosis.
- Annular pancreas, Malrotation, Volvulus, and lesions causing small intestine obstruction:
    - There is bilious vomitus.
- Congenital adrenal hyperplasia with adrenal insufficiency:
    - There is hyperkalemia and evidence of virilization.
- Sepsis and urinary tract infections:
    - There are positive cultures.
- Vomiting with diarrhea suggests gastroenteritis.
- Inborn errors of metabolism:
    - There is recurrent vomiting with alkalosis in urea cycle defects and acidosis in organic academia. There is also lethargy, coma, or seizures.

Management

- It is important to correct dehydration, electrolyte abnormalities and acid base balance before surgery.
- Pyloromyotomy (Ramstedt) is the treatment of choice.

Prognosis

- After surgery, prognosis is excellent.

DUODENAL ATRESIA

CASE

A newborn develops ***bilious emesis*** on the ***first day of life***. Mother is noted to have a large volume of amniotic fluid (***polyhydramnios***) at the time of delivery. An abdominal X-ray in erect position reveals a '***double bubble sign***'.

- Duodenal atresia arises from failure to recanalize the lumen after the solid phase of intestinal development in the 4th and 5th weeks of gestation.

Incidence

- The incidence of duodenal atresia is 1/10,000 births.
- It accounts for 25–40% of all intestinal atresias.
- Half the patients are born prematurely.

Etiology

- Duodenal atresia may be due to many reasons including:
    - An intact membrane obstructing the lumen. Membranous form of atresia is most common. Obstruction is distal to the ampulla of Vater in the majority of patients.
    - A short fibrous cord connecting two blind duodenal pouches.
    - A gap between the non-connecting ends of the duodenum.
    - A windsock web (which is a distensible flap of tissue associated with anomalies of the biliary tract).
- Duodenal obstruction can also be a result of:
    - An extrinsic compression such as of annular pancreas
    - Ladd (peritoneal) bands in patients with malrotation

Clinical findings

- Characteristic features of duodenal obstruction is:
    - Bilious vomiting without abdominal distention
    - Usually noted on the 1st day of life
- Peristaltic waves may be visualized.
- A history of polyhydramnios is present in 50% pregnancies (caused by a failure of absorption of amniotic fluid in the distal intestine).
- Jaundice is present in about 33% of the infants.

Diagnosis

- The diagnosis is suggested by the presence of a **double-bubble sign** on plain abdominal radiographs.
- U/S abdomen reveals pyloric thickness 3-4mm and pylonic length 15-19mm which is diagnostic.

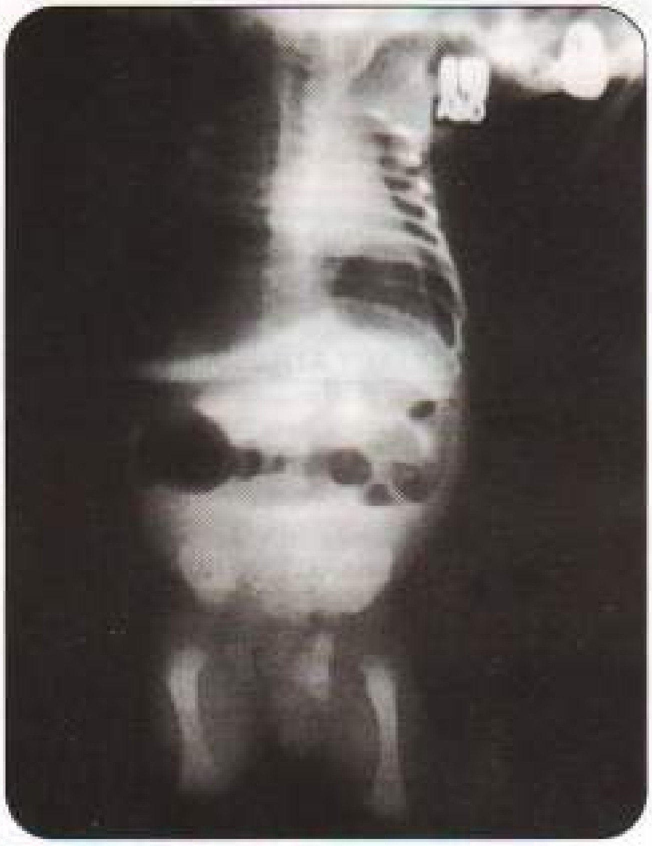


Figure 25.5: Double bubble sign in duodenal atresia.

- Echocardiogram and radiology of the chest and spine should be performed to evaluate for associated life-threatening congenital anomalies (in approximately 30% of infants with duodenal atresia).
- Prenatal diagnosis of duodenal atresia is possible by fetal ultrasonography.

Associations

- Down syndrome (occurs in 20–30% of patients with duodenal atresia)
- Esophageal atresia (10–20%)
- Congenital heart disease (10–15%)
- Anorectal and renal abnormalities (5%)
- Malrotation (20%)

Management

- Initial treatment includes:
  - Nasogastric or orogastric decompression
  - Intravenous fluid replacement
- Definitive correction of the atresia is usually performed after treating the other associated life-threatening anomalies.
- Surgical repair for duodenal atresia is by duodeno-duodenostomy.
- A gastrostomy tube is placed to drain the stomach.
- A transanastomoticjejunal tube is needed until infants start to feed orally.
- If obstruction is due to Ladd bands with malrotation, an operation by division of the abnormal peritoneal folds or bands is necessary (the entire large intestine is placed within the left side of the abdomen and the small bowel on the right)
- Annular pancreas are treated by duodenostomy without dividing the pancreas.

Prognosis

- The prognosis is primarily dependent on the presence of associated anomalies.

BILIARY ATRESIA

CASE

An 8-week-old infant presents with ***jaundice*** since two weeks. He is deeply jaundiced. There is ***hepatosplenomegaly***. ***Stools*** are ***pale***. Ultrasound scan shows ***no gall bladder***. Alanine aminotransferase (ALT) is 300 U/L, glutamyltransferase (GGT) 290 U/L, alkaline phosphatase (ALP) is 600 U/L, ***conjugated bilirubin 6 mg/dL***. Liver biopsy shows ***proliferation of the intrahepatic bile ducts***.

- The obliterativecholangiopathy may cystic (choledochal cyst) or non-cystic fetal and neonatal sclerosing cholangitis.
- The most common form (85% cases), there is obliteration of entire extrahepatic biliary tree above the portahepatis.
- In 2nd type, there is distal segmental bile duct obliteration with patent ducts up to portahepatis and amenable to surgery.
- The neonatal cholestasis is characterized by:
  - Complete and persistent cholestasis (acholic stools) in the first 2 months of life
  - Lack of patency of the extrahepatic biliary tree.
  - Firm to hard hepatomegaly
  - Typical histologic features on liver biopsy
- Biliary atresia occurs in 1:10,000–15,000 births.
- Incidence is equal in both sexes.
- Biliary atresia is due to an insult to the biliary structures in the perinatal period that progress in postnatal period.
- About 30% of cases of extrahepatic biliary atresia are associated with other congenital malformations (especially vascular malformations). Most common association is polysplenia syndrome, which is characterized by situsinversus, interruption of the inferior vena cava, malrotation, levocardia and heterotaxia. .

Clinical findings

- Biliary atresia is presented by jaundice in the newborn period but may be delayed until 2–3 weeks of age.
- Urine is deep yellow but stools are usually pale yellow, gray, or acholic. Yellow color of stools is due to seepage of bilirubin across the intestinal mucosa.
- Hepatomegaly (firm to hard) is common. Later, splenomegaly develops.
- In older patients, there may be pruritis, digital clubbing, xanthoma, and rickety rosary.
- There is poor weight gain, ascites, and bleeding complications.
- It is unlikely to recur within the same family.

Diagnosis

- HIDA scan distinguishes intrahepatic from extrahepatic causes of cholestasis. It is not diagnostic. Pretreatment with phenobarbitone (3–5 mg/kg/day) for 5–7 days is given.
- There is persistent elevation of serum gamma-glutamyltranspeptidase or alkaline phosphatase levels.
- High cholesterol levels may be present.
- There is prolonged prothrombin time.
- Abdominal ultrasonography:
    - Gall bladder is not visualized.
    - It may show choledochal cyst and other intraabdominal anomalies.
- Liver biopsy differentiates intrahepatic causes of cholestasis from biliary atresia.
    - In biliary atresia, there is ductular proliferation with bile plugs and fibrosis while basic liver lobules are intact.
    - In neonatal hepatitis, there is distortion of lobular architecture with inflammatory cells and focal hepatic necrosis and no bile duct changes.
- Surgical exploration is necessary if the diagnosis of biliary atresia cannot be excluded before 60 days of age.

Differential diagnosis

- Neonatal hepatitis
    - Occurs in preterm or low birth weight infants
    - There is familial incidence. Chance of recurrence is 20%.
    - Liver enlargement
- Choledochal cyst
- Intrinsic bile duct obstruction by bile plugs
- Bile duct paucity (Alagille syndrome)

Complications

- Failure to thrive
- Marked pruritis
- Portal hypertension
- Hypersplenism
- Bleeding diathesis
- Rickets
- Ascites
- Hepatic failure
- Death (almost always by age 18–24 months)

Management

- Treatment is surgical.
- Standard surgical procedure is hepatoportoenterostomy (Kasai procedure) or portocholecystostomy (gallbladder Kasai procedure). Surgery should be performed as early as possible (ideal age 6–10 weeks of age due to very low bile drainage after this age.
- Ultimate treatment is orthotopic liver transplantation in patients who:
    - Fail to drain bile after kasai procedure
    - Progress to end-stage biliary cirrhosis despite surgical treatment
- Supportive medical measures are:
    - Vitamin A, D, E, K, and caloric support
    - Choleretics and bile acid-binding products (cholestyramine)
    - Antibiotics to treat ascending cholangitis after surgery

Prognosis

- Death is usually due to liver failure, sepsis, acidosis, or respiratory failure due to intractable ascites.
- After surgery when bile flow is sustained, 5 years survival rate is 30–50%.

MECKEL DIVERTICULUM

CASE

A 16-month-old child presents with several days of ***painless rectal bleeding.*** Stools are of ***currant jelly consistency***. Child is afebrile, alert, and playful. He is slightly tachycardiac, pale and his abdominal examination is normal.

- Meckel diverticulum is an omphalomenteric duct remnant on the antimesenteric border of the distal ileum.
- It occurs in 1.5% of the population.
- In diverticula containing gastric mucosa, acid secretion may produce a contiguous ulcer with bleeding.
- Usual age for bleeding is 6–24 months.

Clinical findings

- Most common presentation is **painless,** sometimes **massive**, lower **GI bleeding** with maroon stools.
- Other common presentations are:
    - Intestinal obstruction
    - Volvulus around the remnant
    - Intussusception
    - Acute diverticulitis
    - Recurrent abdominal pain of childhood
- Majority cause no symptoms.

Diagnosis

- Lateral contrast radiograph
- Umbilical ultrasonography

- Technetium pertechnetate scan identifies diverticula containing gastric mucosa.

Differential diagnosis

- Acute appendicitis
- GI bleeding from vascular anomalies, duplications, bleeding disorder, sloughed juvenile polyp, and other intestinal polyps.
    - Bleeding from a Meckel diverticulum is painless, large volume, purple or maroon, and often causes significant acute anemia. These features help differentiate the rectal bleeding of diverticula from that of a juvenile polyp or fissure.
- Intussusception

Management

- Once diagnosed, treatment is surgical removal of the diverticulum.
- Prognosis is excellent.

INTUSSUSCEPTION

CASE

A 9-month-old boy presents with a four hours history of ***crying*** (intermittent drawing up of his knees to his chest). He has passed several ***bloody stools***, but now he is not passing stool. He is looking very pale. On abdominal examination, there is a ***sausage-like mass*** in right upper quadrant. There is blood upon digital rectal examination.

- This is the most frequent cause of intestinal obstruction in the first 2 years of life.
- More common in males.
- Most common site is ileo-colonic.
- Swelling of the intussuscepted bowel may result in vascular occlusion and bowel necrosis.

Clinical findings

- There are characteristic waves of pain and bilious emesis with interval periods of lethargy.
- Typical symptoms include:
    - Gradual development of pain
    - Bilious emesis
    - Diarrhea followed by bloody diarrhea (currant jelly stool)
    - Fever
    - Sausage-shaped mass in the right lower quadrant

Typical triad

- Colicky abdominal pain (alternating with periods of lethargy)
- Abdominal sausage-like mass
- Currant jelly stools

Diagnosis

- CBC and electrolytes
- Plain abdominal radiograph:
    - Shows specific distribution of bowel gas and signs of obstruction or perforation
- Ultrasonography:
    - Sensitivity 98.5%
    - Specificity 100%
- Air or barium enema :
    - Diagnostic and therapeutic in most infants

Differential diagnosis

- Acute gastroenteritis
- Acute infantile colic
- Testicular torsion in boys
- Strangulated inguinal hernia
- Other causes of intestinal obstruction
    - Lead points for intussusception include polyps, lipomas, lymphoma, swollen lymph nodes, bowel wall hematoma (Henoch-schonleinpurpura), parasites, foreign bodies, or hypertrophied Peyer patches (associated with infection).
- Urinary tract infection
- Serious bacterial illness of any cause (meningitis, septicemia)

Management

- Contrast enema is diagnostic and therapeutic gold standard.
    - It is the first-line therapy for an intussusception.
    - A total of 46% to 80% of intussusceptions can be reduced with enema.
    - Traditionally, a liquid enema was performed under fluoroscopic guidance.
    - However, the current trend is toward air enemas under ultrasonic guidance, which do not use ionizing radiation.
    - The efficacy of the 2 treatments (air enemas and contrast enemas] is similar, and the choice of technique primarily depends on the experience of the attending radiologist.
- When contrast enema reduces intussusception, the child should be closely monitored because 10% of patients will experience intussusception again. The patient is always admitted for 24 hours of observation after reduction. Repeated attempts can be made if the child's condition permits.
- Reduction is considered successful when free reflux of air or barium into the ileum is observed.
- The patient is kept NPO for the first 12 hours, and then the diet is gradually advanced.
- Reduction is contraindicated in patients who have peritonitis or signs of shock.
- Warn parents and staff that high temperature can follow reduction.
- Operation (surgical reduction and/or resection) is mandatory if reduction cannot be accomplished and patient has any of these:
    - Peritonitis
    - Shock
    - Incomplete or unsuccessful reduction

  - Early or multiple recurrences
  - Pathologic lead point
- Uncomplicated, irreducible intussusception may be treated with laparoscopic reduction.
- A delay in definitive diagnosis may lead to greater bowel ischemia and greater likelihood of resection.

HIRSCHSPRUNG DISEASE (Congenital AganglionicMegacolon)

CASE

A 2-year-old boy presents with a history of ***constipation*** since the age of 6 months. He passes one stool per week. Stool softeners are ineffective. Stools are large and hard. There is ***past history of delayed passage of stool at birth***. Physical examination is normal. Rectal examination reveals a large ampulla, poor sphincter tone, and stool in the rectal vault. ***Radiograph (barium enema)*** shows a ***stool-filled megacolon*** (dilated proximal colon and small obstructed distal colon).

- Hirschsprung disease is the congenital absence of ganglion cells both in the muscle layers (Auerbach's plexus) and in the submucosa (Meissner's plexus) of distal rectum and colon.
- The aganglionic segment is narrowed, with dilation of the proximal normal colon.
- This is due to a failure of neural crest cells to migrate to the mesodermal layers from proximal to distal bowel.
- Rectum alone is affected in 30% of the cases.
- Rectosigmoid is usually affected in 44% of the cases.
- Entire colon is aganglionic in 10% of the cases.
- It is four times more common in boys than in girls.
- 10–15% of patients have Down's syndrome.
- It is the most common cause of lower intestinal obstruction in the neonate.
- Overall incidence is 1:5,000 live births.

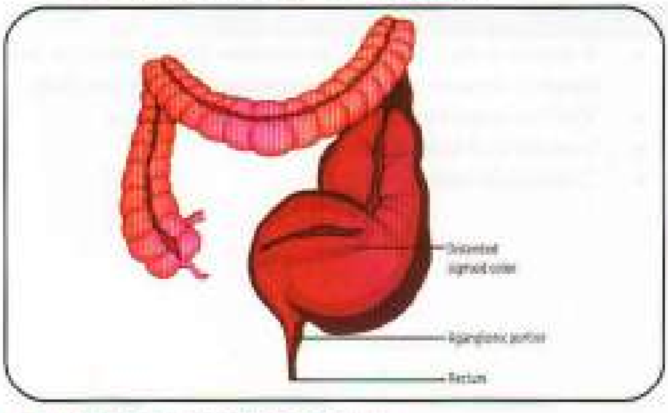


Figure 25.6: Hirschsprung's disease.

Clinical findings

- There is failure of the newborn to pass meconium followed by vomiting, abdominal distension, and reluctance to feed.
- When enterocolitis develops, mucosa of the dilated colonic segment may become thin and inflamed resulting in diarrhea, bleeding, and protein loss. There may be fever. Enterocolitis is mainly due to *Clostridumdifficile, Staphylococcus aureus, anaerobes*, and coliforms. Due to acute inflammatory and ischemic changes, there may be sepsis and colon may perforate especially in the cecal area. Breastfed infants have less severity of the disease.

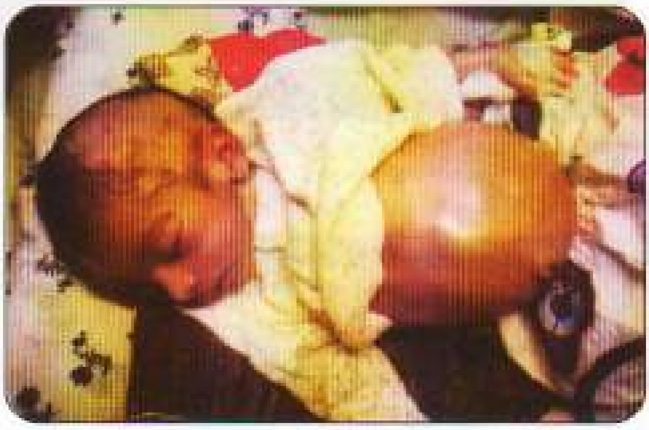


Figure 25.7 : Hirschsprung's disease.

- In infants, there may be alternating constipation and diarrhea. Older child usually have constipation. Stools are ribbon-like. Abdomen is grossly distended and the veins on the abdomen become prominent. Peristaltic waves are visible. On palpation, fecal masses are felt. Due to fecal impaction, there may be intestinal obstruction. Infant fails to thrive.
- On per rectal examination, the anal canal and rectum are empty. There may be a gush of flatus and stool as the finger is withdrawn.

Diagnosis

- X-ray of abdomen shows a dilated proximal colon and absence of gas in the pelvic colon. With barium enema, a transition zone is seen between narrowed distal segment and dilated proximal colon.
- Anorectalmanometry: There is failure of reflex relaxation of the internal sphincter muscle after balloon distension of the rectum.
- On rectal biopsy, ganglion cells are absent in both the submucosal and muscular layers of the involved bowel. With special stains, there is nerve trunk hypertrophy and increased acetylcholinestrase activity.

Differential diagnosis

- Retentive constipation
- Celiac disease

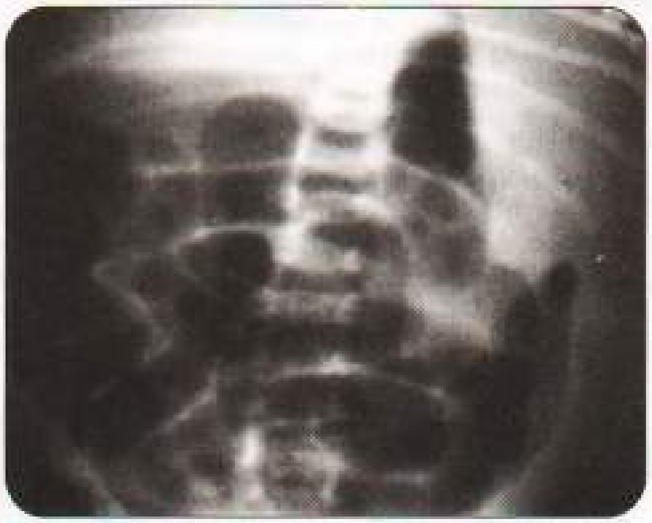


Figure 25.8 : Hirschsprung's disease: A left lateral decubitus film demonstrates multiple dilated loops of bowel and a low bowel obstruction.

Management

- Treatment is surgical with resection of the aganglionic segment.
- Initially colostomy is done.
- A surgical pull-through of ganglionic bowel to the preanal remnant is made.

Prognosis

- After surgery, the prognosis is satisfactory and a large number of patients achieve fecal continence.
- Surgery may have complications e.g. chronic constipation, fecal incontinence, prolapse, perianal abscesses, anastomotic breakdown, enterocolitis, strictures, or fecal soiling.

NEURAL TUBE DEFECTS

- Neural tube defects occur in 1–2 per 1000 newborns.

Types of defects

- The two major types of neural tube defects, anencephaly and meningomyelocele, are caused by failure of the neural groove to fuse completely into a tube by the 28th day of pregnancy.
- Anencephaly represents failure of closure of the cranial neural tube. There is no cranium and have only the most basal portion of the brain. There is profound neurological abnormality and baby usually dies within the first few hours to days of life.
- Meningomyelocele represents failure of closure of the neural tube distal to the brain, leading to hernial protrusion through the vertebral column, as in spina bifida. Lesions may be anywhere along the spine but most commonly occurring in the lumbar area. Failure of development of normal vertebral architecture allows the cord to bulge out of the protective confines of the spine, with resultant loss of neurological function below the level of the lesion.

Clinical findings

- Hydrocephalus due to the associated presence of an Arnold-Chiari malformation of the ventricular system (downward displacement of the hind-brain through the foramen magnum).
- Bladder control may be absent, with consequent recurrent urinary tract infection, reflux, and the need for urinary diversion.
- Bowel function may be lost with severe chronic constipation.
- Clubfoot and other orthopedic problems below the lesion may occur.
- Mental retardation or seizures may occur.

Risk factors

- Some geographic locations
- Higher incidence in poor families
- Maternal age; both teenage mothers and older mothers are at increased risk
- Prenatal exposure to known contributory environmental factors, such as valproic acid, maternal diabetes

Recurrence risk

One affected child	2–3%
Two affected children	10–12%
One affected parent	2–3%

Pre-natal diagnosis

- Elevated alpha-fetoprotein levels in amniotic fluid and in maternal serum.
- Level II ultrasound to examine the fetus for anencephaly or a spinal defect.
- Amniocentesis to determine whether amniotic fluid alpha-fetoprotein and acetyl-choline esterase levels are elevated, because the presence of both of these is more specific for neural tube defects.

Preventive therapy

- Recurrence risk for neural tube defects may be lowered significantly by taking 4 mg of folic acid daily from the time of conception through the time of formation of neural tube (end of first trimester).

Management

- If spinal defect is open, protection from infection and surgical closure is recommended as soon as possible.
- Ventriculoperitoneal shunt for hydrocephalus
- Bladder and bowel care
- Orthopedic management

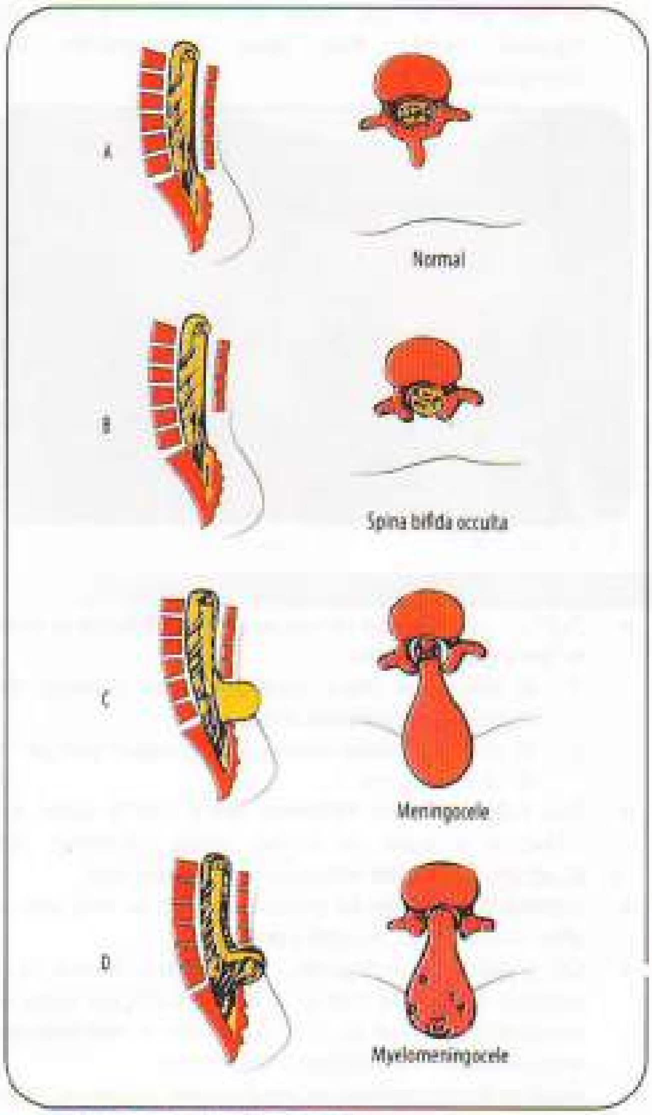


Figure 25.9 : Neural tube defects.

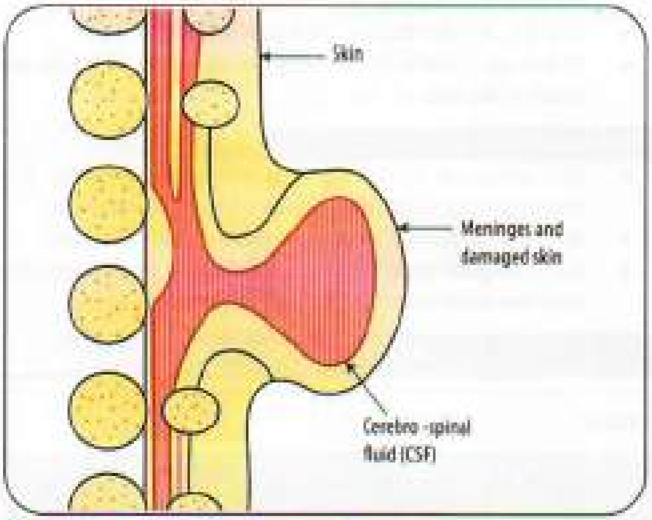
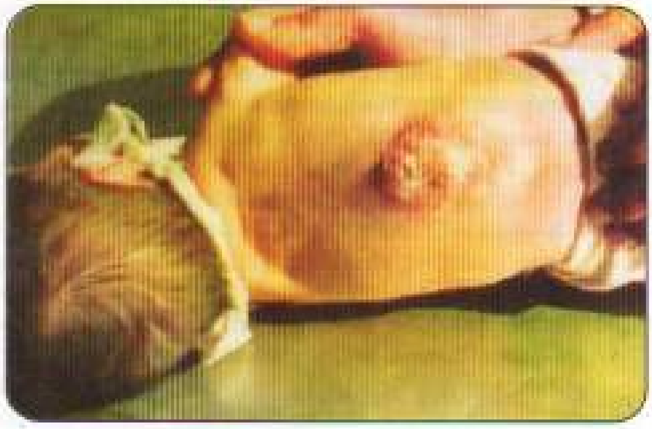


Figure 25.10: Myelomeningocele.



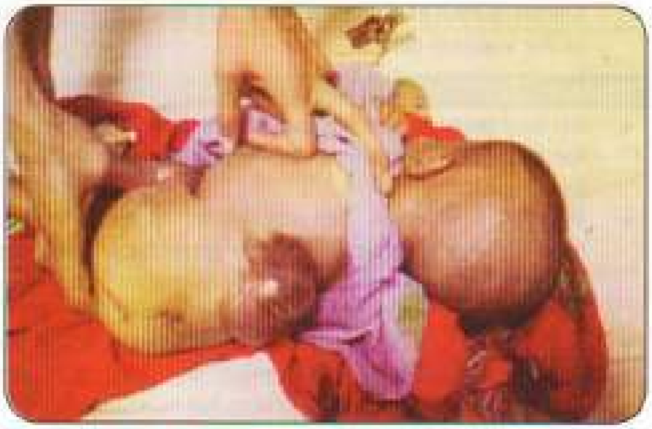


Figure 25.11: A baby with meningomyelocele.

CRYPTORCHISM (undescended testes)

- Cryptorchism (undescended testes) may be unilateral or bilateral. It may be ectopic or true cryptorchism.
- At birth, 30% of premature males and 4.5% of term male newborns have undescended testes.
- Testes descend by the end of third month of age in many infants and at 6 month its incidence drops to 0.8%. It is unilateral in 10% of cases. About 80% of all undescended testes are in the scrotum by the age of one year. Through puberty, further descent may occur.
- If cryptorchism persists into adult life, there is failure of spermatogenesis. Testicular androgen production usually remains normal. There may be torsion, hernia and psychological problems in older children.
- There is a great incidence of malignant neoplasm (seminoma) in testes that remain in the abdomen after puberty.
- ***Ectopic testes*** develop normally but are diverted as they descend through the inguinal canal. Once the diagnosis is established, surgery is indicated.
- ***True cryptorchism***is due to an abnormality in testicular development (dysgenesis). These testes usually have a short spermatic artery, poor blood supply, or both.
- Congenital adrenal hyperplasia should be ruled out in a newborn with bilateral cryptorchism.
- Plasma testosterone levels are obtained after hCG stimulation to confirm the absence of abdominal

testes. To establish the presence of testes and their ability to respond to stimulation, four daily doses of chorionic gonadotropin, 3,000 units/m^2 each, are given intramuscularly. The plasma testosterone should rise to above 200 mg/dl 24 hours after the final dose. In case of testicular failure, a karyotype is indicated to rule out the possibility of a virilized female.

- Examination of testes should be done while the child is in the squatting position or in a warm bath. During palpation of the testes, cremastric reflex may be elicited, resulting in ascent of the testes into the inguinal canal or abdomen. This is called pseudocryptorchism or retractile testes. To prevent this ascent of the testes, the finger first should be placed across the inguinal ring and the upper portion of the inguinal canal.

Management

- No treatment is needed for retractile testes. Prognosis for testicular descent and function in such a case is excellent.
- In case of true cryptorchism, surgical repair (orchiopexy) is indicated for cryptorchism persisting beyond 9–15 month of age. Spontaneous descent of the testis will not occur after 4 months of age.
- Orchiopexy (success rate of 98%) involves an inguinal incision, mobilization of the testis and spermatic cord, and correction of an indirect inguinal hernia
- If a testis is close to the scrotum, a prescrotalorchiopexy can be performed.
- If testes are not palpable then they should be searched with the help of laparoscope having higher yield as compared to abdominal ultrasonography.
- If testes are not palpable then they can be located in the abdomen in 50% of cases and can be brought down by one or two stage procedure.
- If testes found are atrophic and difficult to brought in their actual position, then orchiectomy should be considered.
- Gonadotropin therapy is generally effective only in case of retractile testes.
- Testicular prostheses are considered for older children when the absence of the gonad in the scrotum causes an undesirable psychologic effect.

INGUINAL HERNIA

- Congenital indirecthernias (99%) occur as a consequence of a patent processusvaginalis (a developmental structure important in testicular descent).
- Other types of inguinal hernia are direct (acquired) hernia (0.5–1.0%) and femoralhernia (<0.5%).
- The incidence of inguinal hernia in children is higher in boys (ten times) than in girls.
- Premature infants have an incidence of inguinal hernia about 30%.
- In first year of life, there is 30–40% risk that the inguinal hernia may have incarceration and strangulation.

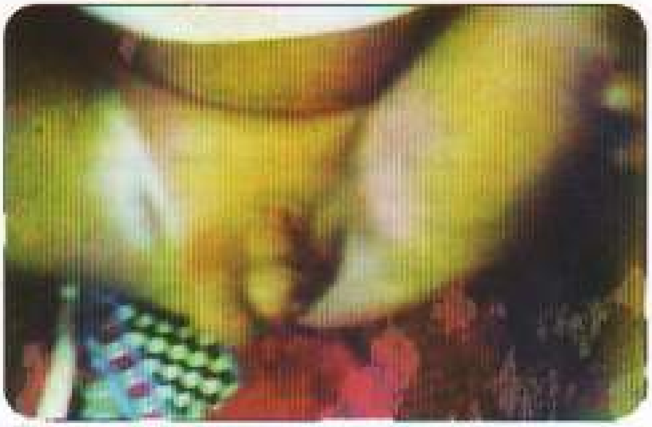


Figure 25.12: A child with right-sided inguinal hernia.

Clinical findings

- Typically, an inguinal hernia appears as a bulge or mass in the inguinal region.
    - In boys, the mass usually extends through the inguinal area into the scrotum.
    - In girls, the mass occurs in the upper portion of the labia majora.
- The bulge or mass becomes more visible when the infant is irritable or during crying, straining, and coughing (increased intraabdominal pressure).
- Inguinal hernia may be present at birth or may appear after some weeks, months, or years.
- On physical examination, an inguinal hernia is a smooth, firm mass that emerges through the external inguinal ring lateral to the pubic tubercle and enlarges with increased intraabdominal pressure.
- Inguinal hernia reduces when the child relaxes or it can be reduced by gentle pressure (posteriorly and then upward toward the peritoneal cavity).
- In boys, the hernia sac contains intestines.
- In female infants there may be an ovary and fallopian tube in the hernia sac.

Management

- The presence of an inguinal hernia in children is an indication for operative repair as early as possible.
- An inguinal hernia does not resolve spontaneously.
- Early surgical repair eliminates the risk of incarceration and the associated potential complications.

ACUTE APPENDICITIS

CASE

A 7-year-old boy presents with a 24 hours history of ***persistent central colicky abdominal pain*** associated with nausea and vomiting. Pain is constant and settled in his lower abdomen and is associated with ***fever*** and

ORGANOPHOSPHORUS POISONING

CASE

A 10-year-old farmer's son was helping his father in the farm. Farmer was ***spraying some insecticide***. The child was well, but while at the farm developed abdominal cramping (***muscle fasciculations***), cough, wheezing (***respiratory distress***), drooling (***salivation***), hyperhidrosis (***excessive sweating***), tearing (***lacrimation***), and increased soiling and urination (***loss of sphincter control***). He has ***bradycardia*** and pin point pupils (***meiosis***).

- Organophosphates and carbamates are the most frequently used insecticides worldwide. These compounds cause 80% of the reported toxic exposures to insecticides.

Pathophysiology

- Organophosphates form an irreversible bond with the enzyme cholinesterase. They act as inhibitors of cholinesterase enzyme. Cholinesterases rapidly hydrolyze the neurotransmitter acetylcholine into inactive fragments. Inactivation of the enzyme acetylcholine to accumulate at the synapse, leading to overstimulation and the disruption of nerve impulses. Skeletal muscle depolarization and fasciculationsoccur secondary to nicotinic stimulation at the motor endplate.
- Muscarinic effects occur at the post-ganglionic parasympathetic synapses, causing smooth-muscle contractions in various organs including the gastrointestinal tract, bladder, and secretory glands. Dysrhythmias are frequently reported; these typically include bradycardia, although tachycardia can also occur.
- Acetylcholine receptors are widely dispersed throughout the CNS. The stimulation of these receptors causes a wide range of effects, including stimulation, seizures, confusion, ataxia, coma, and respiratory or cardiovascular depression.
- Organophosphates are generally highly lipid soluble and well absorbed from the skin, mucous membranes, conjunctiva, gastrointestinal system, and respiratory system.

Clinical findings

- Most symptoms appear within 12–24 hours of exposure.
- Children often ingest home pesticides found in unmarked or poorly stored containers.
- Children can also be exposed while playing in areas recently treated with organophosphate compounds.
- Muscarinic findings may include the following:
    - Salivation, lacrimation, urination, defecation, gastrointestinal cramps, emesis
    - Increased pulmonary and oropharyngeal secretions
    - Sweating
    - Bradycardia
    - Miosis
- Nicotinic findings may include the following:
    - Muscle fasciculations (twitching)
    - Fatigue
    - Paralysis
    - Respiratory muscle weakness
    - Tachycardia
    - Hypertension
- CNS findings may include the following:
    - Anxiety
    - Restlessness
    - Confusion
    - Seizures
    - Coma
    - Central respiratory paralysis
    - Altered level of consciousness and/or hypotonia

Investigations

- Obtain a CBC to rule out infectious causes.
- Serum electrolyte tests may be useful in ruling out electrolyte disturbances.
- RBC cholinesterase tests may reveal a decreased level of activity, which confirms the diagnosis.
- Chest radiography may be performed to evaluate pulmonary edema.
- CT scan head may be required to assess structural lesions if the patient has an altered mental status.
- Obtain an ECG to evaluate for cardiac arrhythmias.

Management

- Decontamination should be done. It is of utmost importance in minimizing continued exposure and to protect providers and other patients from contamination.
- Activated charcoal can be used for gastric decontamination.
- Basic supportive care should be provided e.g. fluid and electrolyte replacement and intubation if necessary.
- Two antidotes are useful:
    - Atropine blocks acetylcholine receptors. It is most effective in reversing muscarinic and CNS effects. Dose is 0.02–0.05 mg/kg/dose repeated after every 10–20 minutes initially along with monitoring of heart rate, temperature, and pupil response. Once the atropine effects are manifest (tachycardia, fever, mydriasis), atropine is given at

the same dose after every 1–4 hours for at least 24 hours. Atropine infusion can be given in dose of 0.02–0.08 mg/kg/hour.

- ○ Pralidoxime–A cholinesterase activator can be used in patients having respiratory muscle weakness as it reverses nicotinic effects. Dose is 25–50 mg/kg/dose in 5–10 minutes and can be repeated after 1–2 hours and then 10–12 hours as needed. It is effective if used early.

Prognosis

- Most exposures related to morbidity and mortality result from anoxic injury due to respiratory failure. Clinical effects range from mild flu-like symptoms with low-level exposures to life-threatening respiratory failure with larger exposures.

CARBON MONOXIDE POISONING

CASE

A 6-year-old child presents in emergency department with ***altered consciousness*** and ***profound muscle weakness***. There is history of ***exposure to exhaust fumes*** from a petrol powered electric generator.

- Toxicity correlates with carboxyhemoglobin level taken very soon after acute exposure but not after lapse of time and oxygen administration.
- Worse with high altitude, high respiratory rate (young infants), pregnancy, lung disease, heart failure.
- Symptoms—headache, confusion, unsteadiness, coma. In severe poisoning, renal, cardiac, vegetative state or lesser permanent CNS injury may result.
- Laboratory findings—proteinuria, glycosuria, increased transaminases, Echocardiogram (ECG) changes.
- Typical red skin color suggests CO poisoning.
- Poorly ventilated furnaces or space heaters produce CO.

Clinical findings

- Symptoms of CO poisoning are usually proportional to the concentration of COHb in the blood.
- COHb concentrations can be measured in all cases.
- Early symptoms are nonspecific and include headache, malaise, and nausea, which are often confused with the flu.
- At higher exposure levels, headaches become severe, and dizziness, visual changes, and weakness may be present.
- Cherry-red mucosal coloring and retinal hemorrhage may also be present.
- Children may experience syncope as a first symptom.
- At high concentrations, coma, seizures, respiratory instability, and death may occur.
- Symptoms usually appear at COHb levels of >15%, toxicity is present at levels of >20%, and severe neurologic effects are universal at levels of >40%.

Differential diagnosis

- Drug overdose
- Depression or other neuropsychiatric disorder

Management

- In addition to general supportive care, treatment of CO poisoning requires the administration of 100% oxygen.
- High concentrations of oxygen shorten the COHb half-life in the blood and tissues.
- The half-life of carboxyhemoglobin in room air is 200–300 minutes. Hyperbaric oxygen (2–2.5 atm) shortens half-life to 30 minutes.
- Severely poisoned patients benefit from hyperbaric oxygen therapy. Indications for hyperbaric oxygen include neurologic symptoms compatible with CO poisoning and a COHb level of >25% in children and pregnant women.
- Nonspecific therapy of anoxic tissue injury in done.
- Dexamethasone may be used if cerebral edema present.
- After a significant exposure, some patients may experience delayed-onset neurotoxicity, which may be permanent. Aggressive early treatment of patients with significant symptoms may diminish the risk of neurologic sequelae.

WARFARIN POISONING

CASE

A 2-year-old child presents with ***hemoptysis*** after ***eating rat poison tablets*** accidently.

- Most rodenticides contain warfarin-type anticoagulants.

Clinical findings

- Many of the patients presenting with rodenticide ingestions are children who ingest such substances unintentionally.
- Common presenting symptoms are:
    - ○ Flank pain with or without frank hematuria
    - ○ Excess bleeding or bruising after relatively minor or no apparent trauma
    - ○ Hemoptysis
    - ○ Epistaxis
- On physical examination, there is evidence of frank bleeding, bruising, or other coagulopathy may be present.

Complications

- Spontaneous intraabdominalhemorrhage
- Hematuria
- Hematemesis
- Spontaneous hemoperitoneum
- Intracerebralhemorrhage
- Death

Differential diagnosis

- Coumarin poisoning
- Diabetic Ketoacidosis (DKA)
- Disseminated Intravascular Coagulation
- Gastrointestinal bleeding
- Rattle snake envenomation

Laboratory investigations

- Prothrombin Time (PT)
- International Normalized Ratio (INR)
- Activated Partial Thromboplastin Time (aPTT)
- Bleeding time
- Platelet count

Management

- Always look for a container, so that the specific product can be determined.
- Secure airway and place Intravenous (IV) lines in hemodynamically unstable patients.
- Give all patients with rodenticide overdose, activated charcoal as soon as possible to prevent further absorption of ingested toxins.
- With anticoagulant overdoses, perform a careful physical examination to look for any sign of bleeding.
- If a coagulopathy is documented, institution of vitamin K therapy is suggested.
- In addition to vitamin K, prothrombin complex concentrates and/or fresh-frozen plasma may be needed to rapidly reverse anticoagulation from warfarin when patients present with life-threatening hemorrhage.
- For small, unintentional ingestions of an anticoagulant rodenticide, repeat PT measurements 24 and 48 hours post ingestion to ensure that no effects on the coagulation pathway are present.

Prognosis

- As long as the proper duration of therapy is used, acute anticoagulant rodenticide overdoses generally resolve uneventfully.
- Deaths usually occur when patients present late after exposure when severe sequelae of anticoagulation have already manifested.

CHAPTER 27

Bone and Joint Disorders

SEPTIC ARTHRITIS

CASE

A 2-year-old child presents with history of ***fever*** and irritability. He has ***refusal to move his right lower extremity***. The knee is tender, edematous, warm, erythematous. There is significantly diminished range of joint movement. There is ***elevated white blood cell count***. The ***joint fluid examination*** shows ***turbid*** fluid containing a predominance of polymorphonuclear leukocytes. X-ray reveals a ***widened joint space***.

- Septic arthritis occurs when bacteria from the circulation enter the joint space. It may also occur from the direct implantation of bacteria due to osteomyelitis or penetrating trauma.
- Septic arthritis may cause destruction of articular cartilage because of a lack of normal nutrients in the synovial fluid or as a result of purulent exudate and increased pressure in the joint space.
- Commonly involved joints are knee (40%), hip (20%), ankle (15%), elbow, wrist and shoulder.

Etiology

- Blood cultures are positive in about 50% of septic arthritis patients.
- Most common pathogens in neonates are *group B streptococcus*, *S. aureus*, and enteric gram-negative rods. In older children main organisms are *S. aureus*, *group A. streptococcus*, *S. pneumonia*, *N.meningitidis*, and *H. influenzae*. *N.gonorrhea* causes septic arthritis in adolescents.

Clinical findings

- The affected joint is warm, swollen, and very painful on movement.
- Septic arthritis may manifest simply as fever and poorly localized pain in the affected extremity.
- Signs and symptoms associated with a septic hip may be limited to a limp or a fixed, flexed hip.

Diagnosis

- **Synovial fluid analysis.**
    - Joint fluid aspiration is necessary for the diagnosis.
    - Aspiration has the additional benefit of decreasing pressure in the joint space.
    - Joint fluid is obtained for gram stain, culture, WBC count, protein and glucose concentration. A white blood cell count exceeding 100,000/μL in the joint fluid indicates a definite purulent infection.
- WBC count in blood is elevated with a shift to the left.
- ESR is usually raised.
- Radiograph usually shows widening of the joint space.
- Ultrasonography demonstrates fluid in joint infections (especially in hip joint).
- MRI may distinguish joint infection from cellulites or deep abscesses.

Differential diagnosis

- Tuberculosis of joint
- Trauma
- Juvenile idiopathic arthritis
- Lyme disease

Management

- Intravenous antibiotics for 3 weeks:
    - Oxacillin plus cefotaxime or an aminoglycoside for neonates
    - Oxacillin plus ceftriaxone for children older than 3 months of age
- Drainage of the joint space by the needle aspiration or surgical excision. In the hip joint, pyogenic arthritis is most easily treated by surgical drainage because the joint is deep and difficult to aspirate.

Prognosis

- It is excellent if the joint is drained early before damage to the articular cartilage.
- If infection is present for more than 24 hours, there may be arthrosis and fibrosis of the joint. There may be damage to the growth plate.

OSTEOMYELITIS

CASE

A 6-year-old child presents with ***fever*** for the last five days. He has ***pain*** and ***difficulty in walking*** in his right leg for 3 days. There is a history of falling from bicycle ten days ago. On examination, there is ***swelling***, warmth and tenderness to his right proximal tibia. He has palpable inguinal lymphadenopathy on the right. He has difficulty bearing weight. He walks with limp. Laboratory studies show WBC 18,000/mm^3. MRI scan shows a small pocket of pus elevating the periosteum and soft tissue swelling of the right proximal tibia (osteomyelitis).

- Infection of the medullary bone with extension to cortical bone.
- Lower extremities most commonly affected, often after trauma.
- Most common agents are *Staphylococcus aureus*and *Streptococcus*.
- There is increased risk for *Salmonella* osteomyelitis in sickle cell disease.
- There is increased risk of *Pseudomonas* after nail punctures through the shoe.
- Infection penetrates across the growth plate in children less than one year causing septic arthritis and long-term growth problems.
- Infection spreads via the periosteum in older children with fused growth plates. Joints are less often involved.

Clinical findings

- Symptoms are fever, irritability, pseudoparalysis, local redness, tenderness and pain.

Diagnosis

- High Erythrocyte Sedimentation Rate (ESR) and White Blood Cell count (WBC).
- Positive blood or bone culture.
- X-ray cannot detect early osteomyelitis or small infections.
- Bone scan and MRI are more sensitive.

Differential diagnosis

- Clinical findings may suggest fracture, bone cyst, bone tumor.
- Other serious infections, inflammatory and autoimmune conditions may initially have the same nonspecific fever and systemic symptoms of osteomyelitis.

Management

- Antibiotic therapy depending on culture and sensitivity for at least 3 weeks.
- Splinting the limb minimizes pain and decreases lymphatic spread.
- Aspiration of the affected bone may be needed for culture and to provide surgical drainage.
- If acute symptoms and signs of osteomyelitis are not resolving within 3 days of initiation of therapy, consider surgical exploration for drainage and debridement.

CLUBFOOT (TALIPES EQUINOVARUS)

- Clubfoot has a multifactorial inheritance.
- It occurs more commonly in males (2:1).
- In 50% of cases, it is bilateral.
- Incidence of talipesequinovarus is about 1:1000 live births.
- An infant with a talipesequinovarus should be examined for associated anomalies e.g. of the spine. Navicular bone is the primary site of deformity.
- There are three features of the classic talipesequinovarus:
  1. Equinus: Plantar flexion of the foot at the ankle joint
  2. Varus: Inversion deformity of the heel
  3. Forefoot varus
- There are three major categories of talipesequinovarus:
  1. Idiopathic it may be hereditary
  2. Neurogenic
  3. Those associated with the syndromes

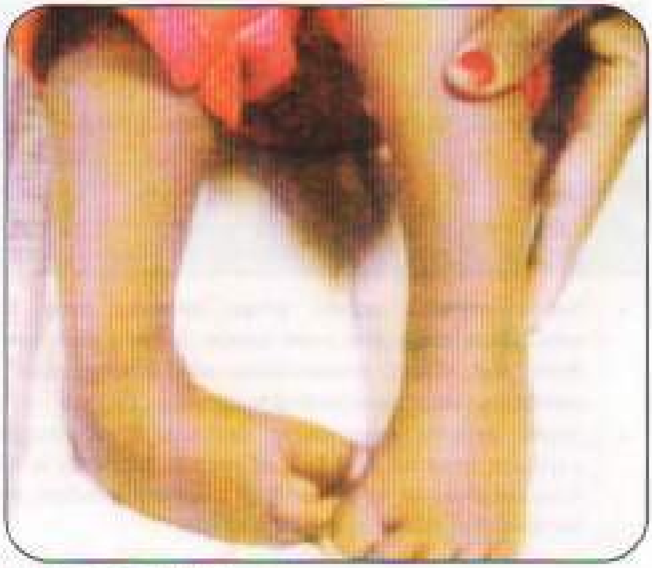


Figure 27.1: Club foot

Management

- Serial plaster casts are the major method of non-operative treatment.
- Operative treatment is performed between 6 and 12 months of age.
- Correction is rapid when treatment is given shortly after birth. Foot is manipulated to stretch the contracted tissues on the medial and posterior aspects. This is followed by splinting to hold the correction.
- If the treatment is delayed even for a few days, feet become more rigid and correction is not rapid. In such a case casts are applied. Forefoot adduction is corrected initially, followed by the correction of the inversion of the heel, and finally the equines of the ankle. For long-term maintenance of correction, a night brace is often used.
- An operative procedure to lengthen the tightened structures of foot is needed in about 50% of children.
- A surgical release and correction is needed in a case of rigid foot resistant to cast treatment.

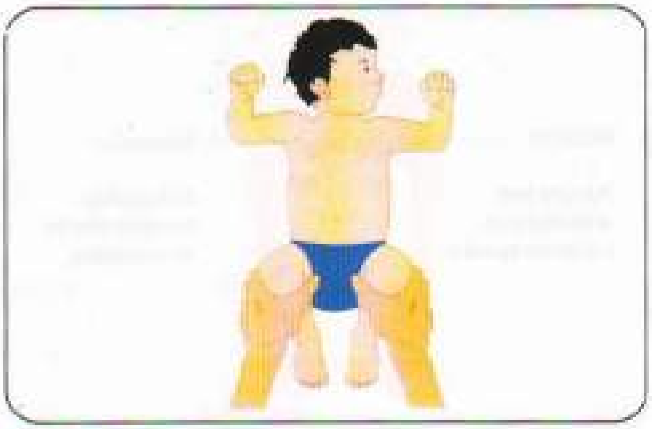


Figure 27.5: Barlow test.

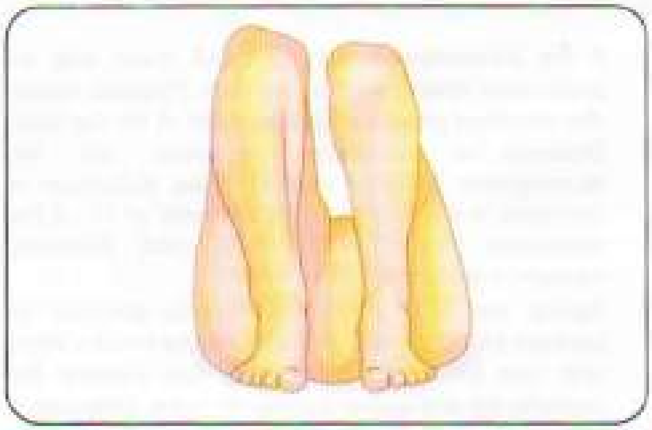


Figure 27.6: For the infant three months or older, Galeazzi's test can be performed. The child is placed in the supine position with the hips and knees bent and the feet flat. The examiner looks for any unevenness between the knees. If one knee is lower than the other, there may be a dislocated hip on the lower side.

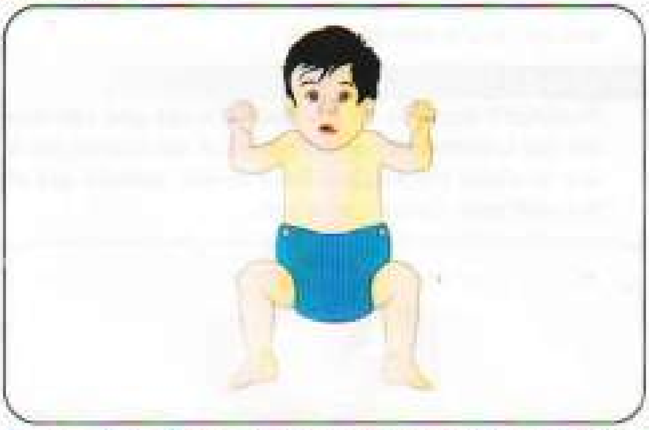


Figure 27.7: Plaster cast in a baby with congenital dislocation of hip joint.

- Dislocation or dysplasia diagnosed in the first few weeks or months of life can easily be treated by splinting, with the hip maintained in flexion and abduction (Pavlik harness). Forced abduction is contraindicated, as this may lead to avascular necrosis of the femoral head.
- It is necessary to place the child in a plaster (hip spica) cast for about 6 months.
- If the reduction is not stable within a reasonable range following closed reduction, open reduction, combined with tightening of the lax capsule in order to maintain reduction, may be necessary.

LEGG-CALVÉ-PERTHES DISEASE

CASE

An 8-year-old boy presents with ***pain*** in his leg for about two months. Pain is becoming worse and his right foot is beginning to turn in while walking. He has developed a noticeable ***limp***.

- Legg-Calvé-Perthes Disease (LCPD) is a hip disorder of unknown etiology.
- It results from temporary interruption of the blood supply to the proximal femoral epiphysis, leading to osteonecrosis and femoral head deformity.
- LCPD is more common in boys than in girls by a ratio of 5 to 1.
- The peak incidence of the disease is between the ages 4 and 8 years.
- Bilateral involvement may be seen in about 10% of the patients.

Clinical findings

- The most common presenting symptom is a **limp** of varying duration.
- Pain, if present, is usually activity related and may be localized in the groin or referred to the anteromedial thigh or knee region.
- Antalgic (painful) gait may be particularly prominent after strenuous activity at the end of the day.
- Hip motion, primarily internal rotation and abduction, is limited.
- A mild hip flexion contracture of 10–20 degrees may be present.
- Atrophy of the muscles of the thigh, calf, or buttock from disuse secondary to pain may be evident.
- There might be an apparent lower extremity length inequality because of an adduction contracture or true shortening on the involved site because of femoral head collapse or growth inhibition.

Differential diagnosis

- Transient synovitis
- JRA
- Septic arthritis

Complications

- Osteoarthritis of hip joint
- Limb length discrepancy
- Permanent femoral head deformity
- Decreased range of movement around the hip joint

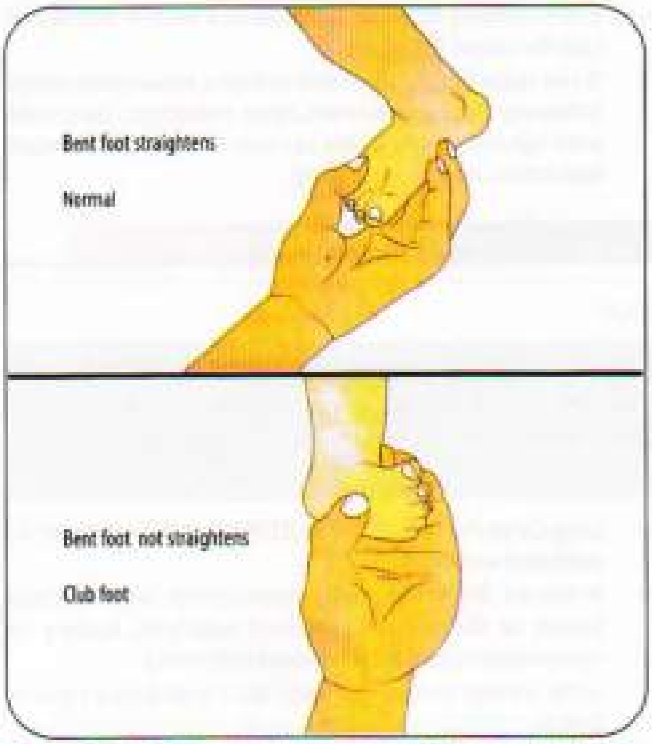


Figure 27.2: Difference between normal foot and club foot.

DEVELOPMENTAL DYSPLASIA OF THE HIP

CASE

A 1 ½-year-old girl presents with limp. Birth history is full term C/S for breech presentation (prolonged labor). On examination, she has positive Barlow and negative Ortolanimaneuvers.

- Hip joints are rarely dislocated at birth.
- They are dislocatable. A dislocatable hip is one in which the hip is within the acetabulum but can be dislocated with a provocative (Barlow) maneuver. Dislocations are postnatal in origin, as they tend to occur after delivery.
- Developmental dysplasia of the hip occurs in approximately 1:1000 live births.
- There is a positive family history in about 10% of the cases.
- There is female predominance (9:1).
- High-risk position is breech position. In breech position, there is extreme hip flexion and limitation of hip movement causing stretching of the capsule and ligament teres. There is posterior un-coverage of the femoral head.
- Cause of the developmental dysplasia of hip joint is multifactorial (physiological and mechanical factors). There is generalized ligamentous laxity causing hip joint instability. There is lack of the development of both the acetabulum and the femur.

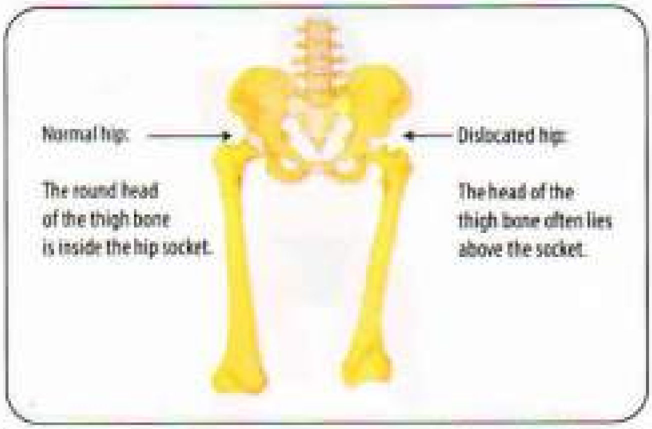

Normal hip:
The round head of the thigh bone is inside the hip socket.
Dislocated hip:
The head of the thigh bone often lies above the socket.

Figure 27.3: Difference between normal hip and dislocated hip.

- If the dislocation is not corrected, there may be progressive dysplasia of the hip joint. Dysplasia means the abnormal growth or development of the hip joint. Dysplasia is completely reversible and hip development becomes normal if the dislocation is corrected in the first few days or weeks of life. If the dislocation persists in an older child, deformity worsens and becomes irreversible.
- Barlow test is a provocative test to dislocate an unstable hip. The examiner stabilizes the infant's pelvis with one hand and then flexes and adducts the opposite hip and applies a posterior force. Dislocatable hip joint is readily felt as a click.
- Ortolani test is a maneuver to reduce a recently dislocated hip. The thigh is flexed and abducted, and the femoral head is lifted anteriorly into the acetabulum. If the reduction is possible, the relocation will be felt as a clunk.
- Ultrasonography accurately assesses the hip stability and acetabular development.

Management

- Treatment depends on the patient's age and whether the hip is sublaxated or dislocated. A sublaxated hip is one in which the femoral head comes partially out of the joint with a provocative test.

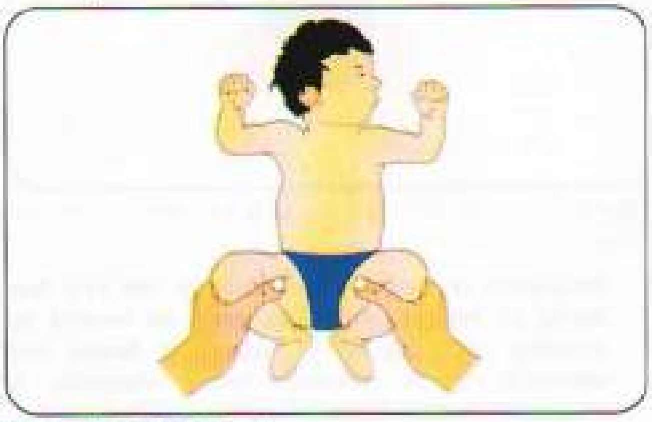


Figure 27.4: Ortolani test.

Diagnosis

- Plain radiographs: Anteroposterior and Lauenstein (frog) lateral views are used to diagnose stage, provide prognosis, follow the course of the disease, and assess results.
    - Decreased size of the ossification center
    - Lateralization of the femoral head with widening of the medial joint space
    - A subchondral fracture
    - Physeal irregularity
- In the absence of changes on plain radiographs, particularly in the early stages of the disease, radionuclide bone scanning with technetium-99m may reveal the avascularity of the femoral epiphysis.
- MRI is sensitive in detecting infarction.
- Arthrography may demonstrate any flattening of the femoral head and the hinge abduction phenomenon with abduction of the leg.

Management

- Goal of treatment: To create a spherical, well-covered femoral head with hip range of motion that is close to normal.
- The methods of treatment include:
    - Observation or no treatment
    - Intermittent symptomatic treatment
    - Containment
    - Late surgery for deformity
    - Late surgery for osteoarthritis
- Patients with severe pain may benefit from a short trial of bed rest and traction.
- Abduction devices have been used to keep the femoral head contained in the acetabulum.

SLIPPED CAPITAL FEMORAL EPIPHYSIS

CASE

A 10-year-old boy presents with a one year history of ***right knee pain***. There is no history of trauma. Pain is not limiting his activities. On examination, he is an ***obese*** child. Right knee appears normal. Examination of the hips reveals no tenderness. There is no gait abnormality. A pelvic radiograph of both hips shows notable ***widening*** and irregularity of the ***proximal femoral epiphyseal growth plate***.

- Slipped Capital Femoral Epiphysis (SCFE) is caused by displacement of the proximal femoral epiphysis due to disruption of the growth plate.

Pathophysiology

- The head of the femur is usually displaced medially and posteriorly relative to the femoral neck.
- The condition occurs in adolescence (most often between 12–15 years of age) and is most common in obese males. Obese children often have retroverted femoral necks that are directed more posteriorly than those of other children.
- The cause is unclear.
- The strength of the perichondrial ring stabilizing the epiphysial area is sufficiently weakened by hormonal changes during adolescence that obesity can cause a fracture through the growth plate.
- Hormonal studies in these children are usually normal. But, SCFE may be associated with hypothyroidism.
- The condition occasionally may occur following a fall or direct trauma to the hip.

Classification

- SCFE is classified clinically as stable or unstable.
    - Stable SCFE: The child is able to bear weight on the affected extremity.
    - Unstable SCFE: The child is unable to bear weight. Inability to bear weight in SCFE correlates with increasing rate of avascular necrosis.

Clinical findings

- Vague symptoms occur in an otherwise healthy child who presents with pain and limp.
- The pain can be referred into the thigh or the medial side of the knee.
- The hip joint should be examined in any obese child complaining of knee pain.
- Consistent finding on physical examination is limitation of internal rotation of the hip.

Diagnosis

- The diagnosis may be clearly apparent only in the lateral radiographic view.
- Common radiographic findings include:
    - Widening and irregularity of the physis
    - A decrease in epiphyseal height in the center of the acetabulum
    - A crescent-shaped area of increased density in the proximal portion of the femoral neck
    - The "blanch sign of Steel" corresponding to the double density created from the anteriorly displaced femoral neck overlying the femoral head
- CT can be used to confirm epiphyseal displacement and accurately measure the amount of displacement
- Bone scanning will show:
    - Increased uptake in the capital femoral physis of an involved hip
    - Decreased uptake in the presence of osteonecrosis
    - Increased uptake in the joint space in the presence of chondrolysis

Complications

- Osteonecrosis or avascular necrosis
- Chondrolysis or acute dissolution of articular cartilage in the hip

Management

- Treatment is same as the treatment of any fracture of the femoral neck.
- The head of the femur is internally fixed to the neck of the femur and the fracture line allowed to heal.

Prognosis

- The long-term prognosis poor as most of these patients continue to be overweight, placing chronic stress on the hip joints.
- The development of avascular necrosis almost has a poor prognosis, because new bone does not readily replace the dead bone at this late stage of skeletal development.
- About 30% of patients have bilateral involvement, which may occur as late as 1–2 years after the one hip joint involvement.

SCOLIOSIS

- Scoliosis is characterized by lateral curvature of the spine associated with rotation of the involved vertebrae.
- Scoliosis is classified by its anatomic location (thoracic, lumbar, and cervical).
- The convexity of the curve is designated right or left. Thus a right thoracic scoliosis would denote a thoracic curve in which the convexity is to the right.
- A mild degree of posterior curvature of the spine is called kyphosis and is normal in the thoracic area. Excessive curvature is pathologic.
- Mild anterior curvature of the spine is called lordosis which is normal in the lumbar and cervical spines.
- Idiopathic scoliosis is four to five times more common in girls than boys. Eighty percent of cases of scoliosis are idiopathic.
- 30% of family members are also affected.
- The disorder is usually asymptomatic.
- Severe curvature can cause pain or loss of pulmonary function in later years.
- Diseases associated with scoliosis include neurofibromatosis, Marfan syndrome, cerebral palsy, muscular dystrophy, poliomyelitis, and myelodysplasia.
- Between 5% and 7% of cases of scoliosis are due to congenital vertebral anomalies such as a hemivertebra or unilateral vertebral bridge.

Clinical findings

- Scoliosis does not cause significant pain.
- If a patient has significant pain, there may be another secondary disorder such as bone or spinal cord tumor.
- Deformity and asymmetry of the rib cage and waistline are apparent with curvatures of 30 degrees or more.
- Less severe curvature may be detected by the **forward bending test**. This is screening examination for scoliosis and performed by having the patient bend forward 90 degrees with the hands joined in the midline. Asymmetry of the height of the ribs or paravertebral muscles on one side indicates the scoliosis.

Diagnosis

- **Radiographs of the entire spine** in the standing position in both the anteroposterior and lateral planes. Primary curvature or a compensatory curvature are seen usually in the right thoracic and left lumbar regions.
- Rotation of the spine may be measured by scoliometer.

Management

- Treatment of scoliosis depends on:
    - Curve magnitude
    - Skeletal maturity
    - Risk of progression.
- Curvatures less than 20 degrees (if not progressing) usually do not require treatment.
- Bracing may be used for curvatures of 20–40 degrees in a skeletally immature child.
- Treatment is required for any curvature that shows progression on repeated radiologic examination.
- Curvatures greater than 40 degrees are resistant to treatment by bracing.
- Thoracic curvatures greater than 60 degrees cause poor pulmonary function and require surgical correction and spinal fusion.

Prognosis

- Compensated small curves that do not progress may be well tolerated throughout life, with minor deformity.
- Early detection allows for simple brace treatment.

OSTEOGENESIS IMPERFECTA

CASE

A 1-year-old baby presents with deformed limbs. On X-ray, there are multiple fractures.

- Osteogenesisimperfecta (OI), or brittle bone disease, is a connective tissue disease (collagen defect) with recurrent bone fractures.
- Inheritance is autosomal dominant.

Clinical findings

- There are four types of OI.
- The classic symptoms include:
    - Blue sclera
    - Conical teeth
    - Multiple bone fractures (particularly arms and legs)
    - Early hearing loss (deafness)
    - Tendency to easy bruising

- Fetal type has intrauterine and perinatal fractures, blue sclerae, thin skin, joint hypermobility, otosclerosis, hearing loss, hypoplastic teeth, wormian bones, normal intelligence.
- Later presentation (tarda type) is less severe.
- Other forms fatal due to severe skeletal deformities and respiratory insufficiency due to thoracic constriction.

Diagnosis

- Intrauterine ultrasound or chorionic villus sampling allows prenatal diagnosis and evaluation of severity.
- In extremely severe (type II) osteogenesisimperfecta, the survey may reveal beaded ribs, broad bones, and numerous fractures with deformities of the long bones. Platyspondylia may also be revealed.
- A definitive diagnosis may be made using a skin punch biopsy. Family members may be given a DNA blood test.

Differential diagnosis

- Child abuse
- Osteopenia secondary to rickets, metabolic renal disease, renal insufficiency, and nutritional deficiencies all promote easy fractures

Management

- No cure for osteogenesisimperfecta
- Active physical rehabilitation
- Fracture management
- Correction of deformity
- Avoidance of injury, regular physical therapy
- Biphosphonates may be helpful
- Bone marrow transplant, growth hormone, gene therapy are experimental

ACHONDROPLASIA

CASE

A six-month-old male child presents with respiratory distress. He is small for age with an upper to lower segment ratio of 1.9. The anteroposterior diameter of thorax is reduced.

- Achondroplasia is the most common form of skeletal dysplasia.
- Frequency is 1 in 20,000 births.
- It is the most common cause of short limb dwarfism.
- Autosomal dominant inheritance

Clinical findings

- The classic phenotype includes:
    - Relative macrocephaly (disproportionately large head)
    - Mid-face hypoplasia
    - Short-limbed dwarfism including Rhizomelic limb shortening (proximal segments of limbs relatively short)
    - Trident-shaped hands (short, broad hands and feet; lack of full adduction of fingers in extension)
- The phenotype is apparent at birth.
- Individuals with achondroplasia are cognitively normal.

Associations

- Neurological complications–hydrocephalus, spinal cord compression at foramen magnum)
- Obstructive sleep apnea
- Recurrent otitis media, conductive or sensorineural deafness

Diagnosis

- Almost all the bones of the skeleton are affected, and hence all parts of the body have bony changes with secondary soft tissue changes. Antenatally it is difficult to diagnose achondroplastic features until the 3rd trimester.
- Radiograph /CT/MRI:
    - Relatively large cranial vault with small skull base
    - The femora and humeri are particularly shortened (rhizomelic shortening)
    - Short pedicle spinal canal stenosis
    - Small squared (tombstone) iliac wings

Management

- No specific treatment is available.
- Orthopedic intervention is necessary for spinal problems including severe lumbar lordosis and gibbus deformity.
- Long bone lengthening surgery.
- Head circumference during infancy must be closely monitored and plotted on a diagnosis-specific head circumference chart. Bony overgrowth at the level of the foramen magnum may lead to progressive hydrocephalus and brainstem compression, and may need neurosurgical opinion.
- For the heterozygous individuals, there is a normal life expectancy if serious complications are avoided.

MARFAN SYNDROME

CASE

A 4-year-old female presents for eye examination. She has arachnodactyly, pectusexcavatum, high arched palate, and enophthalmos. Clinical findings reveal a myopia and exotropia. Cardiac examination shows aortic root dilatation.

Marfan syndrome is a multi system-connective tissue disease with autosomal dominant inheritance which primarily involving skeleton, eyes, and cardiovascular systems.

Clinical findings

- Tall stature (disproportionally long limbs)
- Arachnodactyly
- Pectuscarinatum or excavatum
- Scoliosis
- High, narrow arched palate
- Joint laxity, hypermobile joints
- Pesplanus
- Aortic root dilatation and dissection
- Mitral valve prolapse
- Lens dislocation. Myopia
- Skin striae
- Sex distribution equal

Diagnosis

- Diagnosis is usually clinical but testing shows decreased serum mucoproteins, increased urinary hydroxyproline excretion.
- Genetic testing is available.
- Diagnosis is much more obvious as children grow. Tall stature is the most common reason for investigation.

Differential diagnosis

- Tall stature with abnormal mentation:
    - Cerebral gigantism (Sotos syndrome)
    - Homocystinuria—patients look marfanoid but urinary homocystine is elevated in homocystinuria
    - XXY (Klinefelter syndrome)
    - XYY.
- Familial tall stature
- Some findings shared by Ehlers-Danlos syndrome

Management

- Regular ophthalmologic evaluation and care
- Regular orthopedic evaluation and care, especially to prevent scoliosis
- Regular cardiac evaluation with serial echocardiograms
- β-blockers may reduce the progression of aortic root dilation

CHAPTER 28

Pediatric Drug Therapy

ACETAMINOPHEN (PARACETAMOL)

- Syrup 120 mg/5 ml
- Drops 80 mg/0.8 ml

Dose

- Oral dose is 10–15 mg/kg/dose every 4–6 hours
- Maximum 5 doses/24 hours

Antidote

- Acetylcysteine

Adverse effects

- Blood dyscrasias
- Hepatic necrosis
- Renal tubular necrosis

ACETAZOLAMIDE

- Tablet (diamox) 250 mg

Dose

- Oral and IV dose is 10–25 mg/kg/day divided every 6–8 hours.

Adverse effects

- Adverse reactions: paraesthesia, some loss of appetite, taste disturbance, polyuria, flushing, thirst, headache, dizziness, fatigue, irritability. During long-term therapy, metabolic acidosis and electrolyte imbalance may occasionally occur. This can usually be corrected by the administration of bicarbonate.

ACETYLCYSTEINE

- Acetylcysteine granules 200 mg/sachet (mucolator sachet)

Indications

- Mucolytic
- An antidote of paracetamol overdose

Dose

- For nebulization dose is 3–5 ml of 20% solution + 3–5 ml of 0.9% normal saline (every 4–6 hours, or 6–10 ml of 10% solution.
- To prevent bronchospasm, administer with, or precede acetylcysteine therapy with a bronchodilator).
- Oral dose is 4–10 ml every 6–8 hours.

ACYCLOVIR

- Injection 250 mg
- Tablet (zovirax) 200 mg

Indications

- Herpes simplex encephalitis
- Herpes zoster
- Varicella-zoster
- CMV prophylaxis

Dose

- HSV encephalitis: 30 mg/kg/day IV divided every 8 hours
- Maximum pediatric dose 80 mg/kg/day

Adverse effects

- Headache
- Dizziness
- Rash
- Bone marrow suppression

ACTIVATED CHARCOAL

- Powder form

Indications

- Reduction of absorption of poisons
- Active elimination of poisons

Contraindications

- Poisoning by hydrocarbons with high potential for harm if aspirated
- Poisoning by corrosive substances (may prevent visualization of lesions caused by poison)
- Unprotected airway

Precautions

- Drowsy or unconscious child (risk of aspiration)
- Not effective for poisoning with cyanides, metal salts including iron and lithium.

Dose

- **Reduction of absorption of poisons.** Oral: Neonate, Infant or Child 1 g/kg (maximum 50 g) as a single dose as soon as possible after ingestion of poison.
- **Active elimination of poisons.** Oral: Neonate, Infant or Child 1 g/kg (maximum 50 g) every 4 hours.

Adverse effects

- Black stools, colicky abdominal pain, nausea, vomiting, constipation or diarrhea
- Bowel obstruction, aspiration, pneumonitis

ALBENDAZOLE / ZENTEL

- Tablet 200 mg
- Suspension 200 mg/5 ml

Indications

- An antihelminthic

Dose

- Single oral dose indicated after 2 years of age is 400 mg./40mg/kg

Adverse effects

- GIT disturbances

ALBUMIN HUMAN

- 20% injection 50 ml, 100 ml

Indications

- Used as plasma volume expansion and treatment of hypovolemia

IV dose

- In neonates 0.5–1 g/kg/dose (max 1 g/kg/day)

In infants and children 0.5–1 g/kg/dose (max 6 g/kg/day)

ALFA-CALCIDOL / ONE ALPHA

- Capsule 0.25 mcg/0.5 mcg/1 ml
- Drops 0.2mcg/ml

Indications

- Renal osteodystrophy
- Hypoparathyroidism
- Vitamin D resistant rickets

Dose

- Under 20 kg, 0.05 mcg/kg daily
- Over 20 kg, 1mcg daily

ALLOPURINOL

- Tablet (zyloric) 100 mg, 300 mg

Indications

- Prophylaxis of hyperuricemia associated with cancer chemotherapy

Dose

- Oral dose is 10 mg/kg/day in 2–3 divided doses.

Adverse reactions

- Skin rashes including erythema multiforme
- Renal impairment
- Hepatitis
- Peripheral neuropathy
- Vasculitis
- Uric acid levels decrease in 1–2 days with maximum effect seen in 1–3 weeks.

AMIKACIN

- Injection 25 mg/ml, 50 mg/ml, and 100, 250, mg/2 ml vials.

Indication

- Aminoglycoside antibiotic effective against gram-negative bacilli

Dose

- In Neonates; IM, IV 7.5–10 mg/kg every 8–12 hours

In Children: 15–25 mg/kg/day every 8–12 hours

Adverse effects

- Ototoxicity
- Nephrotoxicity. (Monitor renal function)

AMINOPHYLLINE

- Injection 250 mg/20 ml

Indication

- Apnea of prematurity
- Asthma

Dose

- Loading dose 6 mg/kg IV or oral
- Maintenance dose 2.5–3 mg/kg/dose every 12 hours IV or oral
- As bronchodilator in asthma IV 6 mg/kg (infuse over 30 min), Maintenance continuous IV infusion 0.7–1 mg/kg/hour. OR put 4 ml aminophylline in 100 ml fluid in a burette, then adjust the drops according to the weight of the child e.g. in a child of 10 kg adjust to 10 µd/minute, this will distribute 1 mg/kg/hour.

AMODIAQUINE / BASOQUIN

- Tablet 150 mg
- Suspension 150 mg/5 ml

Indications

- An antimalarial

Dose

- Oral 10 mg/kg stat, then 5 mg/kg 6 hours later, then 5 mg/kg/day as single dose × 2 days.

AMOXICILLIN

- Syrup 125, 250 mg/5 ml
- Capsule 250 mg, 500 mg

- Injection 250, 500 mg/vial

Indications

- Gram-positive pathogens (except staphylococci), *Salmonella, Shigella, Neiserria, E. coli, P. mirabalis*

Dose

- 20–40 mg/kg/day oral divided every 8–12 hours
- Higher doses of 80–90 mg/kg/day for otitis media

Adverse effects

- Skin rash
- Diarrhea
- Abdominal cramping

AMOXICILLIN-CLAVULANATE / AUGMENTIN

- Injection 500 mg amoxicillin/vial
- Syrup 125 mg and DS Syrup 250 mg amoxicillin/5 ml

Dose

- 20–45 mg/kg/day oral divided every 8–12 hours.
- Higher dose for otitis media 80–90 mg/kg/day.

AMPHOTERICIN B

- Amphotericin B Injection

Indications

- An antifungal

Dose

- 0.1–0.25 mg/kg initial dose
- Maintenance dose 0.5 1 mg/kg/day infused IV over 4–6 hours once a day.

Adverse effects

- Hypotension, fever, chills, flushing, augments potassium and magnesium excretion

AMPICILLIN

- Syrup 125, 250 mg/5 ml
- Drops 125 mg/1.25 ml
- Injection 250, 500 mg/vial

Dose

- In newborn<7 days, IV 50 mg/kg/24 hours in divided doses every 12 hours.
- In newborn>7 days 100 mg/kg/24 hours in divided doses every 8 hours.
- Dose for septicemia is IV 100–200 mg/kg/24 hours in divided doses every 4–6 hours.
- Dose for meningitis is IV 200–400 mg/kg/24 hours in *divided doses every 4–6 hours.*

ANTI-HEMOPHILIC FACTOR (HUMAN)

- Factor VIII Injection 250 units/vial

Dose: formula is

- Units required = Body weight (kg) ×0.5 × desired increase in factor VIII (i.e. percent of normal)
- Or 20–50 units/kg/dose administered every 12–24 hours as needed.

ASCORBIC ACID (VITAMIN C)

- Tablet 500 mg
- Drops 100 mg/ml

Indications

- Vitamin C deficiency

Dose

- Oral daily dose is 30–50 mg single dose.
- Dose in scurvy is 100–300 mg/day.

ASPARAGINASE

- Injection (leunase) 5000 IU/vial

Indications

- Used in combination with other anti-neoplastic agents to treat acute lymphoblastic leukemia.

Dose

- IV therapy is 1000 units/kg/day for 10 days or 200 units/kg/day for 28 days.

Adverse effects

- Anaphylaxis, myelosuppression, hepatotoxicity, pancreatitis, GIT upset, azotemia, hyperglycemia, and coagulopathy.

ARTEMETHER / ARTEM

- Oily injection: 80 mg/ml in 1 ml ampoule.

Indications

- Management of malaria

Dose

- Treatment of severe P. falciparum malaria in areas of quinine resistance. Intramuscular injection: Infant or Child over 6 months loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or to maximum of 3 days.

Adverse effects

- Headache, nausea, vomiting, abdominal pain, diarrhea, dizziness, tinnitus.

ARTEMETHER + LUMEFANTRINE

- *Tablet: 20 mg/120 mg*

Indications

- Treatment of uncomplicated malaria caused by P. falciparum alone or with other Plasmodium spp. in areas with significant drug resistance.

Contraindications

- First trimester of pregnancy; history of arrhythmias; history of clinically relevant bradycardia; history of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital prolongation of QTc interval.

Dose

- Treatment of uncomplicated P. falciparum and other Plasmodium malaria. Oral: Infant or Child 5–14 kg initially 1 tablet followed by 5 further doses of 1 tablet each at 8, 24, 36, 48 and 60 hours (total 6 tablets over 60 hours).
- 15–24 kg initially 2 tablets followed by 5 further doses of 2 tablets each at 8, 24, 36, 48 and 60 hours (total 12 tablets over 60 hours).
- 25–34 kg initially 3 tablets followed by 5 further doses of 3 tablets each at 8, 24, 36, 48 and 60 hours (total 18 tablets over 60 hours).
- Over 34 kg initially 4 tablets followed by 5 further doses of 4 tablets each at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours).

Adverse effects

- Abdominal pain, anorexia, diarrhea, nausea and vomiting, headache, dizziness, sleep disorders, palpitation, arthralgia, myalgia, cough, asthenia, fatigue, pruritus and rash.

ASPIRIN (ACETYLSALICYLIC ACID)

- Tablet 300 mg

Dose

- Dose in pain and fever is 10–15 mg/kg/dose every 4–6 hours.
- Dose in rheumatic fever is 60–100 mg/kg/day divided every 6 hours (max 4 g/day).

Contraindications

- Contraindicated in children <16 yrs with chickenpox or flu-like syndrome due to risk of Reye syndrome.

Adverse effects

- Bleeding from gums or GI tract
- Gastric ulcers
- Bronchospasm in asthmatics
- Hearing loss, and Tinnitus

ATROPINE

- Atropine sulfate injection1 mg/ml

Indications

- Antidote to organophosphate poisoning and in treatment of sinus bradycardia

Dose

- In treatment of sinus bradycardia is 0.02 mg/kg (minimum dose 0.1 mg); IV or intratracheal (maximum 0.5 mg); may repeat 5 minutes later, one time.
- Dose as antidote to organophosphorus poisoning is 0.02–0.05 mg/kg every 10–20 minutes until atropine effect appears (tachycardia, mydriasis, fever), then every 1–4 hours for at least 24 hours.

Adverse effects

- Tachycardia, palpitation, delirium, ataxia, dry hot skin, tremor, and impaired vision

AZITHROMYCIN

- Suspension 200 mg/5 ml

Dose

- Oral dose is 10 mg/kg on day 1 followed by 5 mg/kg/day administered once daily for 5 days.

BACLOFEN

- Tablet 10 mg

Indication

- Spasticity associated with upper motor neuron lesions

Dose

- 2–7 years: 10–15 mg/day in three divided doses and increase up to maximum 40 mg/day orally.

Caution

- Avoid abrupt discontinuation, slowly taper to discontinue.

Adverse effects

- Drowsiness, vertigo, and hypotonia

BLEOMYCIN

- Injection 15 mg/ampule

Indications

- Anti-neoplastic medicine

Dose

- 10–20 units/m^2/dose IV (0.25–0.5 units/kg) 1–2 times per week in combination regimens.

Adverse effects

- Interstitial pneumonitis, pulmonary fibrosis, non-productive cough, phlebitis, leukopenia, thrombocytopenia, stomatitis, vomiting, alopecia, hyperkeratosis, desquamation, Raynaud phenomenon.

CALCIUM GLUCONATE 10%

- Injection 9 mg elemental Calcium/ml, 1000 mg/10 ml vial)

Indications

- Hypocalcemia

Dose

- Dose is IV, 1–2 ml/kg/dose (100mg/kg) administered
- over 10 min. Maintenance dose is 2–8 ml/kg/day IV as continuous infusion.

Adverse effects

- Gastrointestinal disturbances, constipation, injection site reactions, fall in blood pressure. Bradycardia, arrhythmia, peripheral vasodilation.

CAPTOPRIL / CAPOTEN

- Tablet 25, 50 mg

Indications

- An ACE inhibitor, anti-hypertensive agent, also used in congestive heart failure

Dose

- Oral dose is 0.15 mg/kg dose every 4–8 hours; dose may be slowly increased to desired effect.
- Maximum dose is 6 mg/kg/24 hours.
- Adverse effects:
    - Renal impairment, neutropenia, immunodeficiency, cough, angioedema, oliguria, hyperkalemia, rashes, and disturbances of taste
    - Adjust dose with renal failure
    - Use with caution in volume depletion

CARBAMAZEPINE

- Tablet (tegretol) 200 mg

Indications

- Anti-epileptic medicine

Dose

- Initial oral dose is 5–10 mg/kg/24 hours in divided doses every 8–12 hours.
- Usual maintenance dose range 20–30 mg/kg/24 hours in children >12 years.
- Maximum dose is 800–1200 mg/24 hours.
- Obtain pretreatment CBC.
- Monitor for renal, hematologic, and hepatic toxicity.

Adverse effects

- Sedation, dizziness, fatigue, ataxia, confusion
- Nausea, vomiting, blurred vision, nystagmus
- Aplastic anemia, neutropenia, leucopenia
- Urinary retention, SIADH
- Platelet dysfunction
- Hepatitis
- Steven-Johnson syndrome

Note

- Phenobarbital, phenytoin, and primidone may decrease carbamazepine levels.
- Carbamazepine may decrease serum levels of phenytoin, benzodiazepines, and valproic acid.

CARBIMAZOLE

- Carbimazole tablet 5 mg (Neomercazole)

Indications

- Carbimazole is an anti-thyroid agent. It is indicated in adults and children in all conditions where reduction of thyroid function is required. Such conditions are: hyperthyroidism, preparation for thyroidectomy in hyperthyroidism, therapy prior to and post radio-iodine treatment.

Dose

- The usual initial daily dose is 15 mg per day adjusted according to response. (0.25 mg/kg)

CEPHALEXIN

- Syrup 125 mg/5 ml, 250 mg/5 ml
- Drops 125 mg/1.25 ml)

Indications

- A first generation cephalosporin active against *S. aureus, Streptococcus, E. coli, Proteus, Klebsiella*

Dose

- Oral dose is 25–100 mg/kg/24 hours in divided doses every 6 hours

CEPHRADINE

- Syrup 125 mg/5 ml, 250 mg/5 ml
- Injection 250 mg/vial, 500 mg/vial)

Indications

- A first generation cephalosporin, active against *S. aureus, Streptococcus, E. coli, Proteus, Klebsiella*

Dose

- Oral, IV, IM dose is 50–100 mg/kg/24 hours in every 6 hours.

CEFACLOR

- Syrup 125, 250 mg/5 ml, Drops 125 mg/ml

Indications

- A second generation cephalosporin active against*S. aureus, Streptococcus, Pneumococcus, H. influenzae, E. coli, Proteus, Klebsiella.*

Dose

- Oral dose is 20–40 mg/kg/24 hours in divided doses every 8 hours.

CEFUROXIME (ZINACEF)

- Injection 250, 750 mg/vial

Indications

- Indications are same as cefaclor.
- It is a second generation cephalosporin.

Dose

- Dose is IM, IV 50–100 mg/kg/24 hours in divided doses every 6–8 hours.

CEFOPERAZONE

- Injection 500 mg, 1 g/vial

Indications

- A third generation cephalosporin active against gram-positive and negative pathogens.

Dose

- IV dose is 100–150 mg/kg/24 hours in divided doses every 8 hours.

CEFTRIAXONE

- Injection 250 mg, 500 mg, 1 g/vial

Indications

- A third generation cephalosporin active against gram-positive and negative pathogens; no anti-pseudomonal activity.

Dose

- Dose is IM, IV 50–75 mg/kg/24 hours (not to exceed 2 g) in a single dose or divided doses every 12 hours.
- In meningitis dose is 80–100 mg/kg/24 hours (not to exceed 4 g) in divided doses every 12 hours.

CEFOTAXIME

- Injection 250, 500 mg, 1 g/vial

Indications

- A third generation cephalosporin active against gram-positive and negative pathogens; no anti-pseudomonal activity.

Dose

- Dose is IM or IV.
- In newborn<7 days old 100 mg/kg/24 hours in divided doses every 12 hours.
- In newborn>7 days old 150 mg/kg/24 hours in divided doses every 8 hours.
- In children 100–200 mg/kg/24 hours in divided doses every 6–8 hours.
- In meningitis 200 mg/kg/24 hours in divided doses every 6 hours.

Adverse effects

- May cause hypersensitivity reactions in penicillin-sensitive patients.
- Adjust dose in patients with renal failure.

CEFTAZIDIME

- Injection 500 mg, 1 g/vial

Indications

- A third generation cephalosporin active against gram-positive and negative pathogens, also possesses anti-pseudomonal activity.

Dose

- Dose is IM or IV.
- In newborn<7 days age 100 mg/kg/24 hours in divided doses every 12 hours.
- In newborn>7 days age and children 100–150 mg/kg/24 hours in divided doses every 8 hours.
- In meningitis 150 mg/kg 24 hours in divided doses every 8 hours.

CEFIXIME

- Syrup 100 mg/5 ml ; 200mg / 5ml

Indications

- A third generation cephalosporin active against *Streptococcus, H. influenzae, M. catarrhalis, N. gonorrhoeae*.

Dose

- Oral dose is 8 mg/kg/24 hours in divided doses every 12–24 hours (maximum 400 mg/24 hours).

Note

- First generation cephalosporins do not cross the blood-brain barrier and thus are ineffective for treatment of infections within the CNS.
- Second generation cephalosporins are more active against gram-negative bacteria such as H. influenzae type b, N. gonorrhoeae, and enteric gram-negative bacilli. Some second generation cephalosporins may cross the blood-brain barrier e.g. cefuroxime.
- Third generation cephalosporins are less active against gram-positive cocci but are more active against most strains of enteric gram-negative bacilli.

CHLORAL HYDRATE (CEDATE)

- Chloral hydrate syrup 500 mg/5 ml

Indications

- Used for sedation and sleep

Dose

- Oral dose for sedation is 25 mg/kg/24 hours in divided doses every 6–8 hours.
- Oral dose for sleep is 25–75 mg/kg/dose.

CHLORAMPHENICOL

- Syrup 125 mg/5 ml
- Injection 1 g/vial

Indications

- Antibiotic active against many gram-positive and negative bacteria, *Rickettsia, Chlamydia, Mycoplasma, Salmonella.*

Dose

- Oral dose is 50–100 mg/kg/24 hours in divided doses every 6 hours.
- IV dose is 100 mg/kg/24 hours in divided doses every 4 hours (over 15–30 minutes).

Adverse effects

- Adverse reaction in newborn is gray-baby syndrome.
- Weekly hematocrit or hemoglobin and reticulocyte count are mandatory. Idiosyncratic aplastic anemia occasionally occurs without warning and may be fatal.
- Use only when specifically indicated.

CHLOROQUINE (RESOCHIN)

- Tablet 150 mg base
- Syrup 50 mg/5 ml
- Injection 200 mg/5 ml vial
- Indications same as amodiaquine

CHLORPHENIRAMINE

- Syrup (avil) 15 mg/5 ml
- Injection 22.7 mg/2 ml

Dose

- Oral anti-allergic dose is 1-2 mg/kg/24 hours in divided doses every 6 hours.

CHLORPROMAZINE

- Syrup (largactil) 25 mg/5 ml
- Injection 25 mg/ml

Indications

- Treatment of psychosis, mania, nausea, and vomiting.

Dose

- For sedation oral dose is 2 mg/kg/24 hours in divided doses every 4–6 hours or when necessary. IM, slow IV dose is 2 mg/kg/24 hours (maximum single IV dose is 12 mg).

Adverse effects

- Hypotension, tachycardia, arrhythmias, pseudo-parkinsonism, tardive dyskinesia, akathesia, dystonias, constipation, nasal congestion, dry mouth, and malignant hyperpyrexia.
- Diphenhydramine may be antidote.

CIMITIDINE

- Injection 200 mg/2 ml vial
- Syrup 200 mg/5 ml

Indications

- H_2 antagonist receptor competitively inhibits secretion of gastric acid. It is indicated in duodenal and gastric ulcers.

Dose

- In newborn, oral, IM, IV dose is 5–10 mg/kg/24 hours every 8–12 hours; in infants and children oral or IV dose is 20–40 mg/kg/24 hours in divided doses every 4–6 hours.

CIPROFLOXACIN

- Tablet 250 mg, 500 mg
- Infusion 100 mg/100 ml
- Syrup 125 mg/5 ml, 250 mg/5 ml

Indications

- Quinolone antibiotic active against *P. aeruginosa, Shigella, Salmonella, Campylobacter, N. gonorrhoea, H. influenzae, some S. aureus and strep spp.*

Dose

- Oral dose is 20–30 mg/kg/24 hours in divided doses every 8–12 hours, usual max dose is 1.5 g/kg/24 hours. IV dose is 4–15 mg/kg/24 hours in divided doses every 8–12 hours (in infusion over 60 min).

CLARITHROMYCIN

- Suspension 125 mg/5 ml, 250 mg/5 ml
- Injection 500 mg/vial
- Tablet 250 mg, 500 mg

Dose

- Oral dose is 15 mg/kg/24 hours in divided doses every 12 hours.

CLONAZEPAM

- Drops (rivotril) 0.1 mg/drop
- Tablet 0.5 mg, 2 mg

Indications

- A benzodiazepine with selective anticonvulsant effect.

Dose

- Oral dose: 0.01–0.03 mg/kg/day in 2–3 divided doses (maximum 0.05 mg/kg/day).

Adverse effects

- Tachycardia, chest pain, drowsiness, fatigue, impaired memory and coordination, depression, blurred vision, nausea, vomiting, dry mouth, hypersalivation, anorexia, bronchial hypersecretion, respiratory depression, physical and psychological dependence.

CO-TRIMOXAZOLE

- Trimethoprim-Sulfamethoxazole (TMP-SMX)
- Syrup TMP 40 mg SMX 200 mg
- DS Syrup TMP 80 mg SMX 400 mg

Indications

- Antibacterial active against *Shigella, Pneumocystis carinii, Legionella, Chlamydia*.

Dose

- Oral dose in infants >2 months old and children is 8–10 mg trimethoprim (TMP) + 40–60 mg sulfamethoxazole(SMX)/kg/24 hours in divided doses every 12 hours.
- Do not use in infants less than 2 month old.
- Reduce dose in severe renal insufficiency.

Adverse effects

- Rash, nausea, Stevens-Johnson syndrome
- May cause bone marrow depression

CORTICOTROPIN (ACTH)

- ACTH gel (acthar gel) 40 IU/5 ml vial

Indications

- ACTH used in infantile spasms, diagnostic agent in adrenocortical insufficiency, acute exacerbation of multiple sclerosis, severe muscle weakness in myasthenia gravis.

Dose

- Dose in infantile spasms is 5–160 units/kg/day for 1 week–12 months as IM gel.

CYCLIZINE

- Syrup 12.5 mg/5 ml
- Injection 50 mg/ml

Indications

- An antiemetic

Dose

- 3 mg/kg/day oral

Adverse effects

- Blurred vision, drowsiness, and dry mouth

CYCLOPHOSPHAMIDE

- Tablet (endoxan) 50 mg
- Injection 200 mg, 500 mg, 1 gm/vial

Indications

- Antineoplastic alkylating agent

Dose

- Dose in nephrsotic syndrome is oral 2–3 mg/kg/day.
- Maintain high fluid intake to avoid hemorrhagic cystitis and consider administration of mesna.

CYCLOSPORIN

- Tablet (neoral)

Indications

- An immuosuppressant agent

Dose

- Oral initial dose is 14–18 mg/kg/dose.
- Maintenance dose is 5–15 mg/kg/day divided every 12–24 hours, usually tapered to 3–10 mg/kg/day.

Adverse effects

- Hypertension, hirsutism, tremor, nephrsotoxicity, gingival hypertrophy, leg cramps, GIT discomfort, acne, seizure, and headache.

CYTARABINE

- Injection (cytosar) 100 mg/vial

Indications

- An antineoplastic and antimetabolite.Used to treat leukemia and lymphoma.

Dose

- Induction IV 100–200 mg/m^2/day for 5–10 days or until remission.
- Maintenance IV 70–200 mg/m^2/day for 2–5 days at monthly intervals.

DAUNORUBICIN

- Injection 20 mg/vial

Indications

- An antineoplastic agent used in treatment of ALL and myeloblasticleukemia.

Dose

- Remission induction for ALL (combination therapy): 25–45 mg/m^2 on day 1 every week for 4 cycles (max total 300 mg/m^2).
- Avoid in patients with heart failure or arrhythmias.
- Irreversible cardiotoxicity may occur if total dose exposure exceeds 300 mg/m^2 in children >2 years, 10 mg/kg in children <2 years.

Adverse effects

- Alopecia, red discoloration of urine, nausea, vomiting, diarrhea, GIT ulceration, stomatitis, myelosuppression, extravasation related tissue ulceration and necrosis, CCF, hyperuricemia, hepatotoxicity.

DEFEROXAMINE

- Injection (desferal) 500 mg/vial

Indications

- A chelating agent for treatment of iron intoxication.May be used for aluminum toxicity.

Dose

- IV dose is 10–15 mg/kg/hours infusion (maximum 12 g/day), SC 20–40 mg/kg/day over 8–12 hours via portable infusion device.

Adverse effects

- Local pain and induration, flushing, hypotension, tachycardia, fever, hearing loss, blurred vision, cataracts.
- Contraindicated in renal failure or acute anuria unless concomitant hemodialysis is used.

DESMOPRESSIN ACETATE (DDAVP)

- Tablet (minirin) 0.1 mg, 0.2 mg

Indications

- A synthetic analog of vasopressin indicated as:
  - Replacement therapy in the management of central diabetes insipidus
  - Control of bleeding in certain types of hemophilia
  - Primary nocturnal enuresis

Dose

- Nasal insufflation dose is 5–30 µg/24 hours divided every 12–24 hours. IV 5 µg/day in 1–2 doses. Dose determined by patient response.
- Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 0.2 to 1.2 mg. A suitable starting dose in adults and children is 0.1 mg thrsee times daily. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 0.1 mg to 0.2 mg thrsee times daily.

Adverse effects

- Facial flushing, dizziness, hypertension, headache, hyponatremia, abdominal cramps, and excessive water retention.

DEXAMETHASONE

- Injection 4 mg/ml, 20 mg/5 ml vial
- Tablet 0.5 mg

Indications

- Adrenal corticosteroid used systemically and locally for acute and chronic inflammation, allergic, neoplastic and autoimmune diseases, cerebral edema, septic shock, *H. influenzae meningitis*.

Dose

- Anti-inflammatory; oral, IM, IV 0.08–0.3 mg/kg/day divided every 6–12 hours.
- Bacterial meningitis; IV 0.6 mg/kg/day divided every 6 hours for days 1–4 of antibiotics.
- Cerebral edema; oral, IM, IV loading dose 1–2 mg/kg, then 1–1.5 mg/kg/day divided every 4–6 hours.

Adverse effects

- Insomnia, nervousness, increased appetite, hypertension, hyperglycemia, GI hyperacidity, cataracts, adrenal suppression, and poor growth.

DIAZEPAM

- Injection 10 mg/2 ml vial
- Tablet 2 mg, 5 mg, and 10 mg

Indications

- A benzodiazepam with anticonvulsant, anxiolytic and muscle-relaxant effects.

Dose

- In status epilepticus: 0.1–0.5 mg/kg/dose IV (slowly, as controlled 'push' injection); may be repeated at 3–5 minutes intervals; follow with continuous infusion of 0.3 mg/kg/hour (dilute in saline to 0.1 mg/ml), do not exceed 1–2 mg/kg/minute IV infusion rate.
- Infusion may be made by putting 2 cc (10 mg diazepam) in 100 cc of D/Saline in a burette, then adjust the drops according to the weight of the patient, e.g. in a 10 kg child giving 10 □g/minut distribute 0.1 mg/kg/hour.

Adverse effects

- Rapid IV administration is associated with bradycardia, apnea, cardiac arrest, respiratory arrest, hypotension, and cardiovascular collapse.

DIGOXIN

- Injection 0.250 mg/ml
- Tablet 0.25 mg
- A cardiac glycoside with rapid onset of action and half-life of approximately 48 hours

Indications

- Systolic heart failure
- Supraventricular tachy-arrhythmias

Dose

- 0.03–0.05 mg/kg
- Maintenance dose is 0.01 mg/kg.
- Administer TDD over 24 hours as thrsee divided doses: 1st dose = ½ TDD, 2nd dose = ¼ TTD administered 8 hours after 1st dose, and 3rd dose = ¼ TDD administered 8 hours after 2nd dose.
- Begin maintenance dosage 24 hours after 1st fraction of digitilizing dose.
- Administer IV dose over 10 minutes.
- Utilize maintenance dose schedule for nonacute arrhythmia and CCF conditions.

Adverse effects

- Feeding intolerance
- Vomiting
- Diarrhea
- Bradycardia

- Depression
- Vertigo
- Blurred vision
- Diplopia
- Photophobia
- Yellow or green vision and lethargy
- Toxic cardiac effects are prolongation of PR interval, sinus bradycardia or S-A block, atrial or nodal ectopic beats, and ventricular arrhythmias
- Toxicity enhanced by hypokalemia

DIMENHYDRINATE (GRAVINATE)

- Injection 50 mg/ml
- Syrup 12.5 mg/5 ml

Indications

- Antiemetic

Dose

- Oral 4–6 mg/kg/day every 6 hours or 0.5 mg/kg/dose.

DIMERCAPROL

- Injection in oil: 50 mg/ml in 2 ml ampoule

Indications

- Acute heavy metal poisoning by antimony, arsenic, bismuth, gold, mercury, possibly thallium; adjunct (with sodium calcium edetate) in lead poisoning.

Contraindications

- Not indicated for iron, selenium or cadmium poisoning; severe hepatic impairment (unless due to arsenic poisoning).

Precautions

- Hypertension; renal impairment; any abnormal reaction such as hyperpyrexia should be assessed; peanut allergy (peanut oil in injection); G6PD deficiency.

Dose

- Heavy metal poisoning. IM: Infant or Child 2.5–3 mg/kg every 4 hours for 2 days, 2–4 times on the third day, then 1–2 times daily for 10 days or until recovery.

Adverse effects

- Hypertension, fever, tachycardia, malaise, nausea, vomiting, abdominal pain, salivation, lacrimation, sweating, burning sensation in the mouth, thrsoat and eyes, injection site pain, headache, muscle spasms, tingling of the extremities, feeling of constriction in throat and chest.

DOBUTAMINE

- Injection 250 mg/20 ml

Indications

- β-adrenergic inotropic agent used for short-term treatment of cardiac failure due to depressed cardiac contractility.
- Short-term support of neonates with shock and hypotension.

Dose

- 2.5–25 μg/kg/minute
- Maximum dose is 40 μg /kg/minute.
- Suggested drip administration = [6 × infant's weight (kg) × (desired dose (μg/kg/minute)/desired fluid rate (ml/hour))] = mg dobutamine per 100 ml solution.
- For example, 1 kg to get 5 μg/kg/minute if IV rate is 3 ml/hours; [6× 1 kg x (5 μg/kg/minute)/(3 ml/hour)] = 10 mg dobutamine added to 100 ml solution.
- Unlike dopamine, dobutamine does not cause release of endogenous nor-adrenaline, nor does it have any effect on dopaminergic receptors, which are two features that render dobutamine a useful alternative if dopamine-associated tachycardia is undesirable.
- Contraindicated in idiopathic hypertrophic subaortic stenosis.
- Correct hypovolemia before use.
- Continuously monitor heart rate and blood pressure.

Adverse effects

- Hypotension (in setting of hypovolemia), arrhythmias, tachycardia (with high doses), cutaneous vasodilation, hypertension, and dyspnea. Extravasation may cause tissue necrosis.

DOMPERIDONE (MOTILIUM)

- Suspension 1 mg/ml

Indications

- Regurgitation, nausea, vomiting

Dose

- 0.25–0.5 mg/kg 3–4 times daily

Adverse effects

- Raised serum prolactin

DOPAMINE

- Injection 200 mg/5 ml

Indications

- Adjunctive therapy for shock refractory to adequate volume replacement.
- Dose related stimulation of dopaminergic, beta, and alpha-receptors with result-ant dose related inotropic and vasopressor effects.

Dose

- Renal (low) dose: 2–5 μg/kg/minute IV
- Cardiogenic (intermediate) dose: 5–15 μg/kg/minute IV
- Pressor (high) dose: >20 μg/kg/minute IV

- Suggested drip administration = [6 ×infant's weight (kg) × [desired dose (µg/kg/minute)/desired fluid rate (ml/hour)]] = mg dopamine per 100 ml solution.
- Maximum dose is 20–25 µg/kg/minute IV.

DOXORUBICIN

- Injection 10 mg/5 ml, 20 mg/10 ml

Indications

- An antineoplastic used for various tumor types.

Dose

- 35–75 mg/m^2/dose repeat every 21 days; or 20–30 mg/m^2 repeat every week; or 60–90 mg/m^2 given as continuous infusion over 96 hours every 3–4 week.
- Contraindicated in CCF and cardiomyopathy.

Adverse effects

- Cardiotoxicity, alopecia, hyperuricemia, stomatitis, esophagitis, mucositis, nausea, vomiting,thrombocytopenia, lacrimation, extravasation tissue necrosis, and phlebitis.

EPINEPHRINE (ADRENALINE)

- Adrenaline injection 1:1000 and 1: 10,000 solution

Indications

- Use in the treatment of cardiac arrest, bronchospasm, and anaphylactic reactions.

Dose

- Neonates; IV, intratracheal 0.01–0.03 mg/kg (0.1–0.3 ml/kg of 1: 10,000 solution) every 3–5 minutes.
- Infants and children; SC 0.01 mg/kg (0.01 ml/kg/dose of 1: 1000 solution), IV 0.01 mg/kg (0.1 ml/kg of 1: 10,000 solution) (Maximum 1 mg), intra-tracheal 0.1 mg/kg/dose (0.1 ml/kg of 1: 1000 solution) (Maximum 0.2 ml/kg).

Adverse effects

- Tachycardia, hypertension, nervousness, restlessness, irritability, headache, tremor, weakness, nausea, vomiting, and acute urinary retention.
- Contraindications are hypertension, diabetes, and hyperthyroidism.

ERYTHROMYCIN

- Tablet 250 mg, 500 mg
- Syrup 200 mg/5 ml
- Drops 100 mg/2.5 ml
- Injection 1 g/vial

Indications

- A macrolide anti-microbial agent especially effective against atypical organisms.

Dose

- Oral dose is 30–50 mg/kg/24 hours in divided doses every 6 hours. IV dose is 15–20 mg/kg/24 hours divided every 6 hours in infusion.
- Do not administer IM (causes pain and necrosis).
- Cholestatic jaundice occurs with estolate, although hepatotoxicity is uncommon.

ETHAMBUTOL

- Tablet 400 mg

Indications

- Treatment of tuberculosis, in combination with other drugs.

Contraindications

- Optic neuritis; severe renal impairment.

Precautions

- Visual disturbances and renal impairment. Patients should report visual disturbances immediately and discontinue treatment.

Dose

- Oral dose is 20 mg/kg/24 hours as a single daily dose.
- Poorly penetrates CSF.
- It is contraindicated in children below 6 years of age because of inability to assess color vision (optic neuritis).

Adverse effects

- Optic neuritis (reduced visual acuity and red/green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness)), gout, peripheral neuritis (especially in legs).

ETHOSUXIMIDE

- Syrup (zarontin) 200 mg/5 ml

Indications

- An anti-convulsant agent used for treatment of absence, myoclonic, and akinetic epilepsy.

Dose

- Oral dose is 15–40 mg/kg/24 hours in divided doses every 12–24 hours. Maximum 1.5 g/day.

Adverse effects

- Sedation, lethargy, nausea, vomiting, anorexia, abdominal pain, leukopenia, thrombocytopenia, and aplastic anemia.

FERROUS SULFATE

- Syrup 26 mg elemental iron/5 ml
- Drops 25 mg elemental iron/ml

Indications

- Iron deficiency anemia

Dose

- Oral dose in iron deficiency anemia is 3–6 mg/kg/day of elemental iron.

Adverse effects

- Constipation, diarrhea, and GI irritation

FILGASTRIM (G-CSF)

- Injection (neupogen) 30 MIO/UE and 0.3 mg/ml syringe

Indications

- Granulocyte colony-stimulating factor reduce duration of neutropenia.

Dose

- 5–10 µg/kg/dose daily for 14 days, may be discontinued if absolute neutrophil count remains >1000/mm^3 for 3 consecutive days.

Adverse effects

- Hypotension, vasculitis, fever, exacerbation of pre-existing skin disorders, increased uric acid, thrombocytopenia, medullary pain, hematuria, and proteinuria.

Cautions

- Malignancy with myeloid characteristics

FLUDROCORTISONE

- Tablet (florinef) 0.1 mg

Indications

- A mineralocorticoid for maintenance therapy in 21-OH deficiency.

Dose

- Dose is 0.05–0.30 mg daily.

FOLIC ACID

- Tablet 5 mg

Indications

- Treatment of megaloblasticanemia

Dose

- Oral dose is 50–150 µg/day
- In folate deficiency 1 mg/day

FUROSEMIDE (LASIX)

- Tablet 20 mg, 40 mg
- Injection 20 mg/2 ml

Dose

- Oral dose; start with 2 mg/kg/dose.
- IV dose; start with 1 mg/kg/dose; if needed, increase progressively to 6 mg/kg/dose, with an interval of at least 2 hours between doses.
- Duration of action is about 2 hours when given IV.

Adverse effects

- Dehydration, hypochloremic alkalosis, potential ototoxicity, prerenalazotemia, hyperuricemia, agranulocytosis, anemia, thrombocytopenia, interstitial nephritis, and pancreatitis.

GENTAMICIN

- Injection 20, 40, 80 mg in 2 ml ampule
- Injection 10 mg in 1 ml ampule

Indications

- An aminoglycoside indicated against gram-negative aerobic bacteria.

Dose: IV dose

- In newborn<7 days, 2.5 mg/kg/dose every 12 hours.
- In newborn>7 days, 5–6 mg/kg/24 hours divided every 12 hours.
- In infants and children, 5–7.5 mg/kg/24 hours divided every 6–8 hours.

Adverse effects

- Vestibular and auditory ototoxicity, and renal toxicity

GENTION VIOLET

Indications

- Treatment of cutaneous and mucocutaneous infections (kills Candida, staphylococcal species, and some vegetative gram-positive bacteria

Dose

- Apply 0.5–2% solution with cotton to lesion 2–3 times/day for 3 days.
- Do not swallow.

Adverse effects

- Burning, local irritation or sensitivity reactions

GLUCAGON

- Injection Glucagon

Indications

- Treatment of hypoglycemia

Dose

- Neonates; 0.3 mg/kg/dose IV, IM, SC (max 1 mg); Children 0.025–0.1 mg/kg/dose (maximum 1 mg), may repeat in 20 min.

Adverse effects

- Nausea, vomiting, and hypersensitivity reactions.

HALOPERIDOL (SERENACE)

- Tablet 0.25 mg, 1.5 mg, 5 mg, 10 mg
- Injection 5 mg/ml

Indications

- Indicated in psychosis

Dose

- Oral: Start 0.25–0.5 mg/day in 2–3 divided doses, then increase weekly by 0.25–0.5 mg daily based on response to maximum 0.15 mg/kg/day.

Adverse effects

- Drowsiness, restlessness, anxiety, extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome.

HEPARIN

- Injection 5000 units/ml

Indications

- An anti-coagulant

Dose

- Dose for flushing IV lines, 1–10 units/ml solution used sparingly as needed. Dose in thromboembolic disorders 50–100 units/kg/dose administered every 4–6 hours based on achieving desired prolongation of patient's clotting time.

Adverse effects

- Heparin induced thrombocytopenia, hemorrhage, fever, urticaria, vomiting, elevated liver enzymes, osteoporosis, and alopecia.
- Antidote is protamine sulfate (1 mg/100 U of heparin given in the previous 4 hours).

HUMAN GROWTH HORMONE

- Injection 4 IU/vial (Norditropin), Humatrope 5mg/viral

Dose

- Human growth hormone 0.06 mg/kg (0.15 IU/kg) 3 times/week.

Adverse effects

- Local lipoatrophy, hypothyroidism, and pain in hip or knee.

HYDROCORTISONE

- Injection 100 mg/2 ml, 250 mg/2 ml, 500 mg/4 ml.

Indications

- Used in septic shock.Adjunct in the emergency treatment of anaphylaxis.

Dose

- IV in septic shock 35–50 mg/kg/dose IV bolus, then 50–150 mg/kg/day IV divided every 6 hours for 2–3 days.

Adverse effects

- Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses. Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, edema, hypertension, hypokalemia, hyperglycemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behavior).

IBUPROFEN

- Syrup 100 mg/5 ml
- Tablet 200, 400 mg

Indications

- An NSAID having analgesic and anti-pyretic activities.

Dose

- As anti-pyretic, oral 10–15 mg/kg/dose at intervals of 4–6 hours (maximum. 40–60 mg/kg/24 hours).
- For juvenile rheumatoid arthrsitis 30–70 mg/kg/24 hours in divided doses every 4–6 hours.

Adverse effects

- Gastritis, platelet dysfunction, and possible compromise in renal function.

IMIPENEM/CILASTATIN

- Injection 250 mg, 500 mg/vial

Dose

- IV in neonates 40–60 mg/kg/24 hours in divided doses every 12 hours; in children 60–100 mg/kg/24 hours in divided doses every 6 hours.

Adverse effects

- Pruritis, vomiting, diarrhea, seizures, hypotension, elevated LFTs, blood dyscrasias, and penicillin allergy.

IMMUNE GLOBULIN, INTRAVENOUS (IVIG)

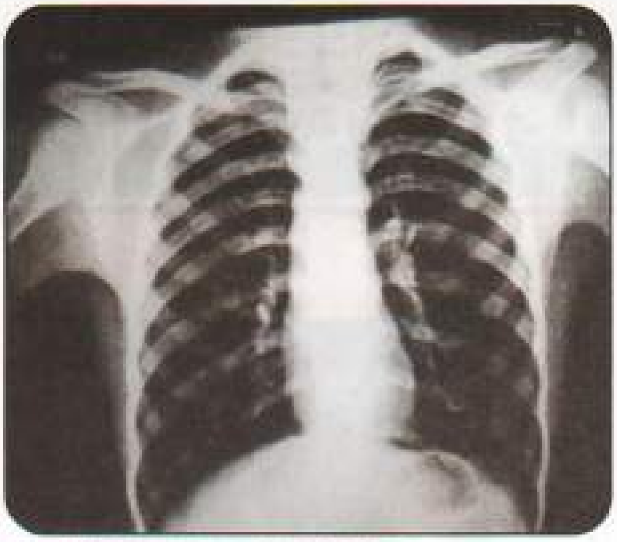
- Injection 250 mg/5 ml, 500 mg/10 ml, 2.5 g/50 ml

Indications

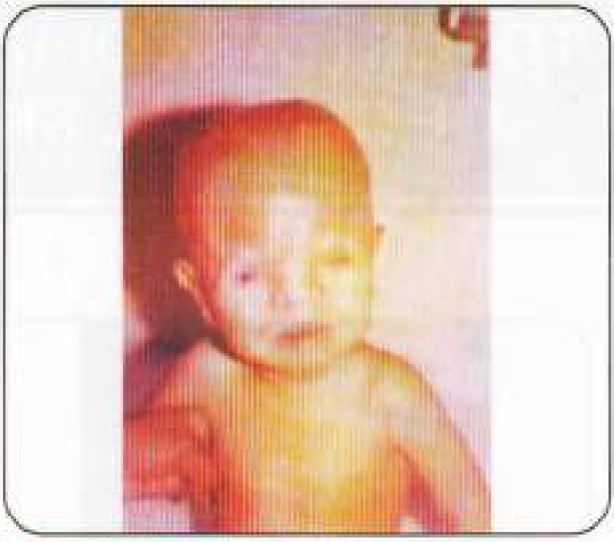
- Immunodeficiency syndrome
- ITP
- Acute bacterial or viral infections in immuno-compromised or neutropenic patients
- GB syndrome

Dose

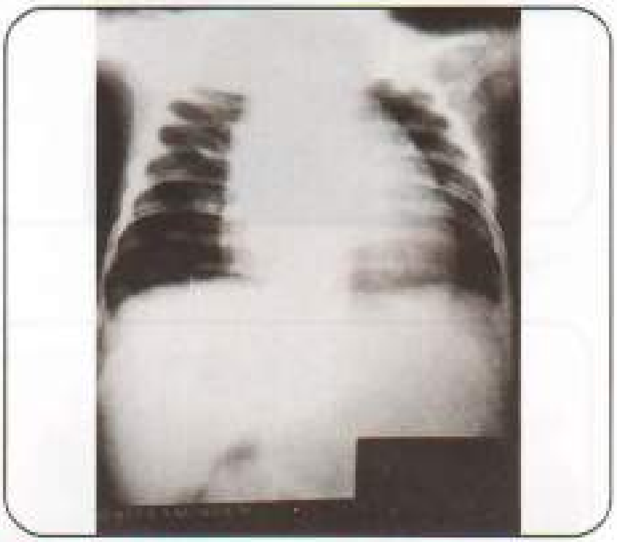
- Neonates 500–750 mg/kg once.
- Immunedeficiency syndromes 100–400 mg/kg/dose every 2–4 weeks.
- ITP 1000 mg/kg/dose for 2–5 consecutive days then every 3–6 weeks.
- GB syndrome 1 g/kg/day for 2 consecutive days.
- Doses should be based on ideal body weight not total body weight.



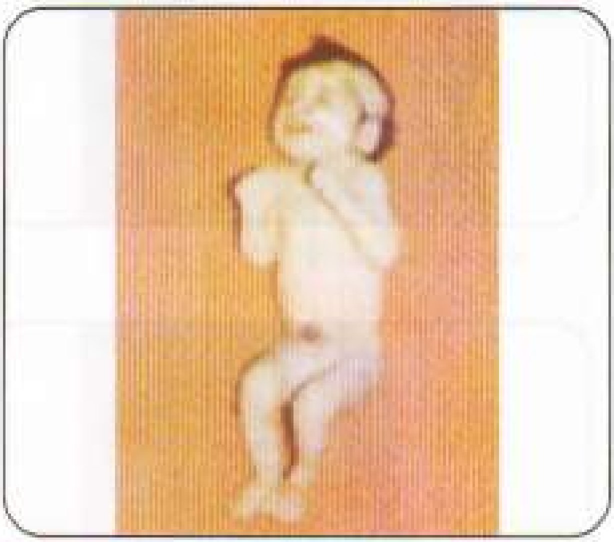
X-ray chest showing hyperinflation in asthma



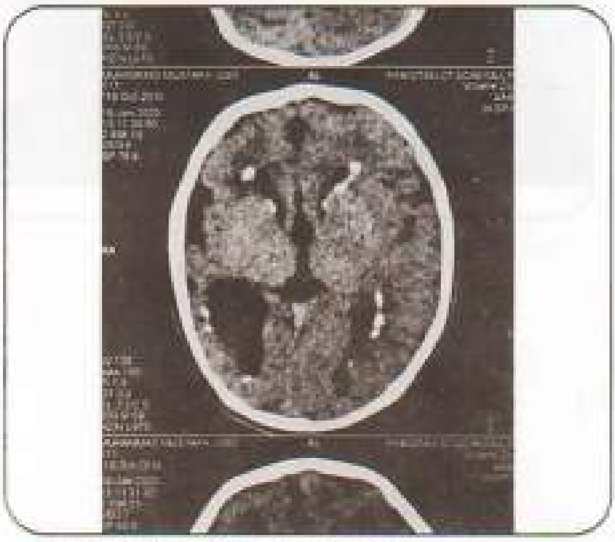
Ectodermal dysplasia with absent hair and eye lashes.



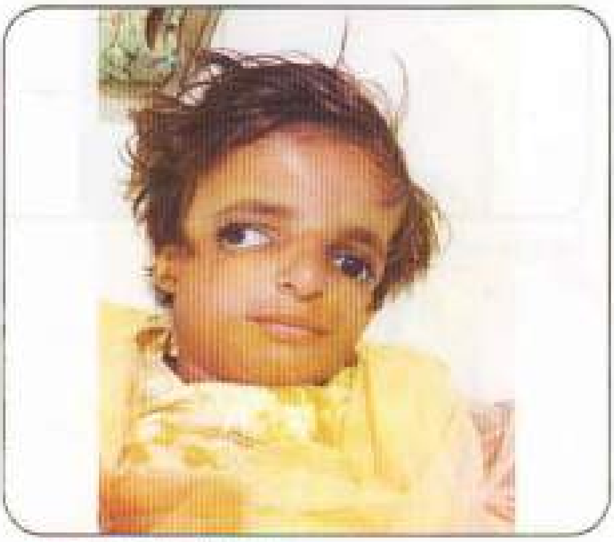
Cardiomegaly in a case of congenital heart disease.



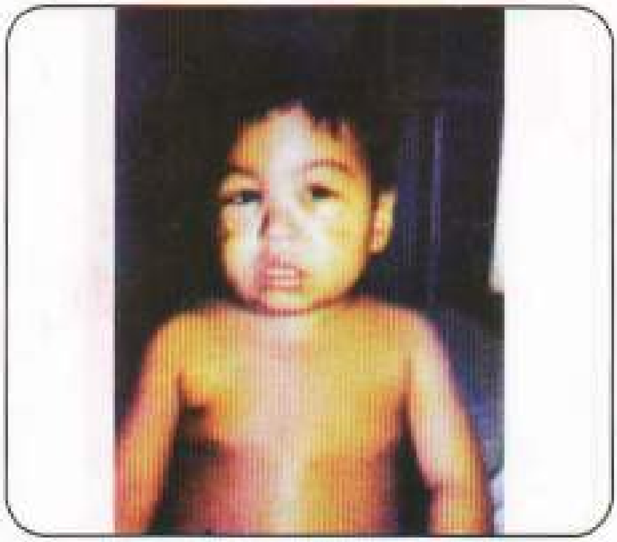
Tetanus neonatorum.



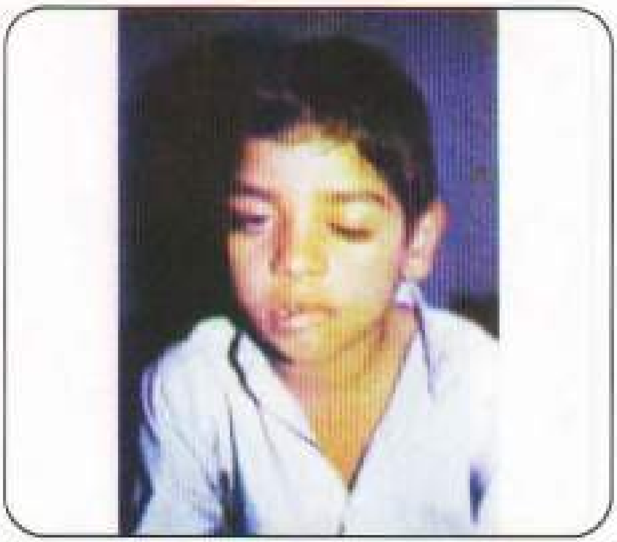
Periventricular calcification in CMV



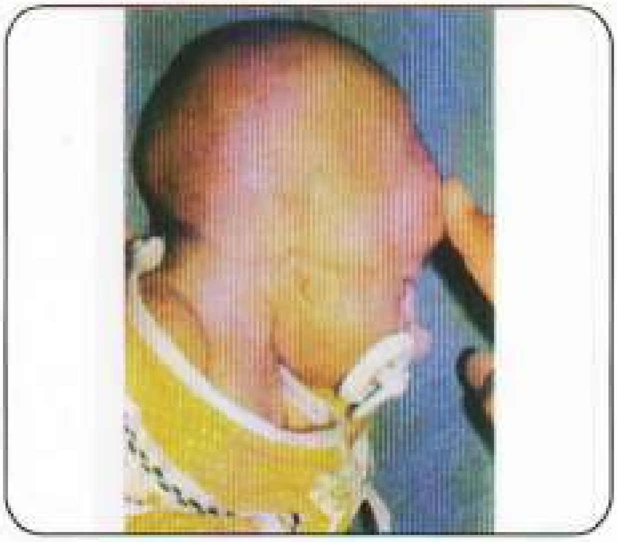
Treacher-Collin syndrome



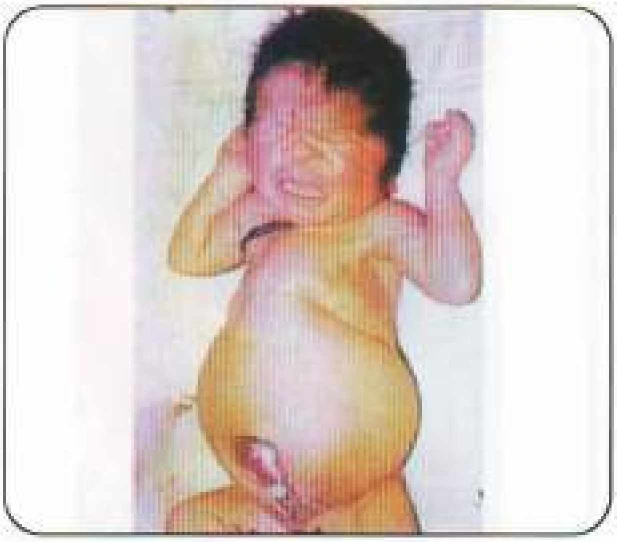
Nephrotic syndrome.



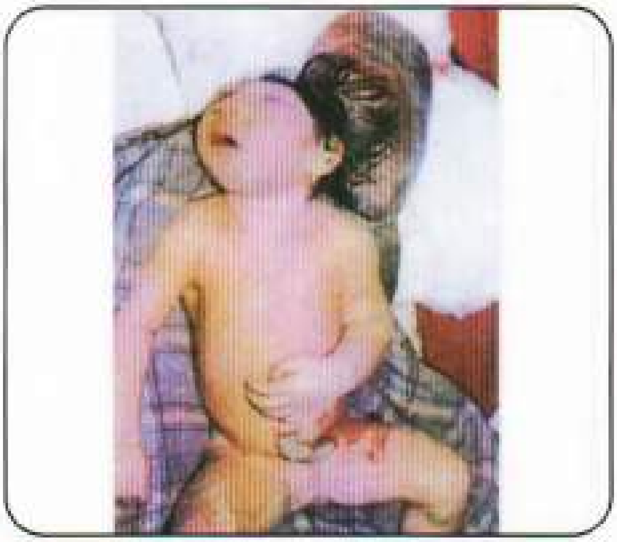
Facial palsy of lower motor neuron type, right side of face.



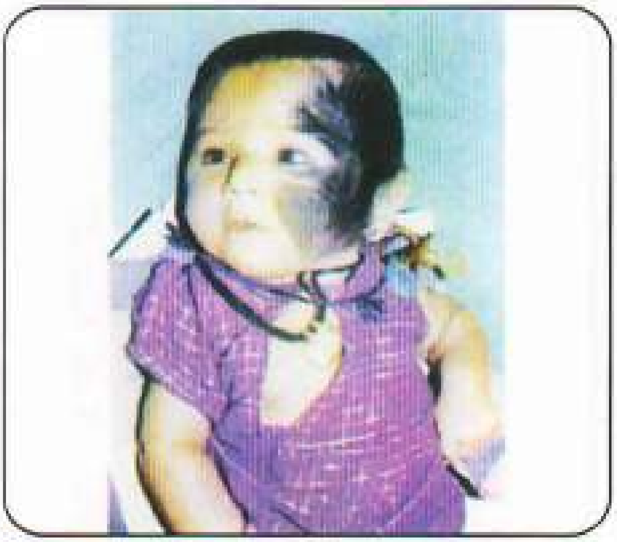
Absence of pinna and malformed ear.



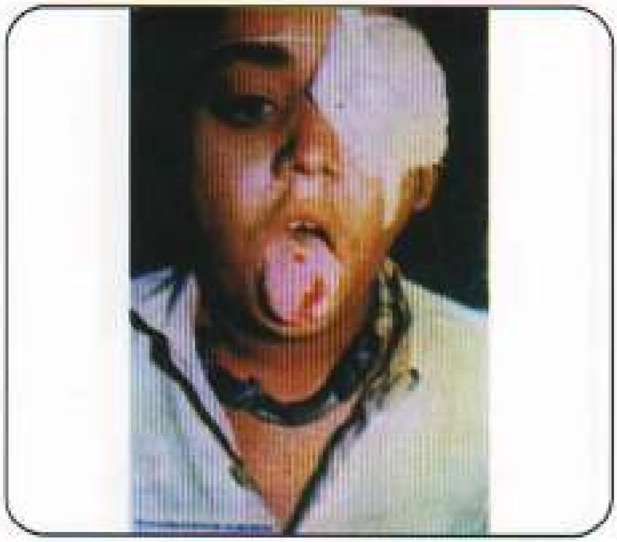
Severely deformed chest in asphyxiating thoracic dystrophy of Jejune.



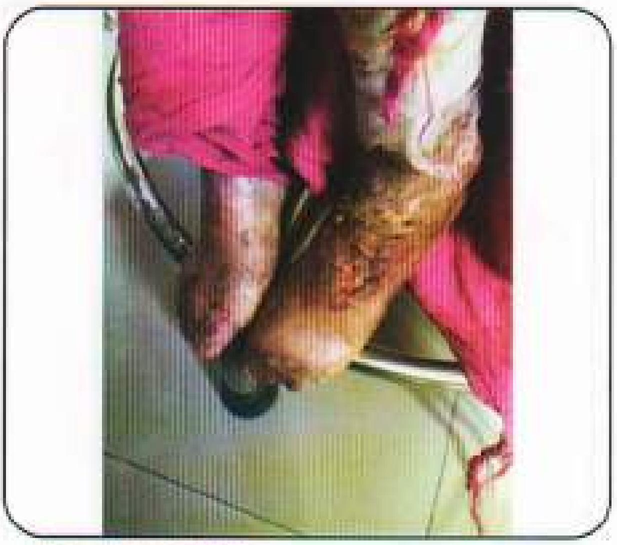
Anencephaly.



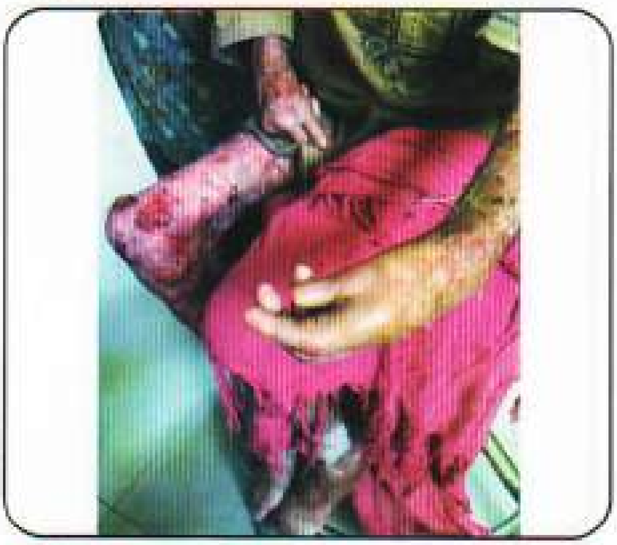
Hairy nevus.



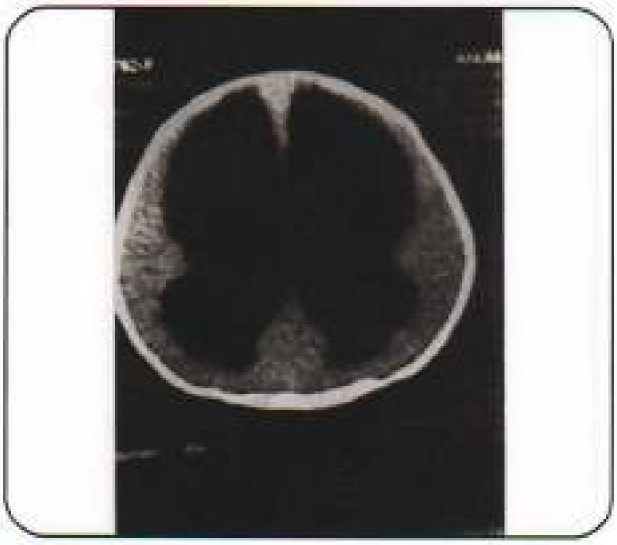
Acute leukemia. Patient having tongue ulceration and corneal sloughing.



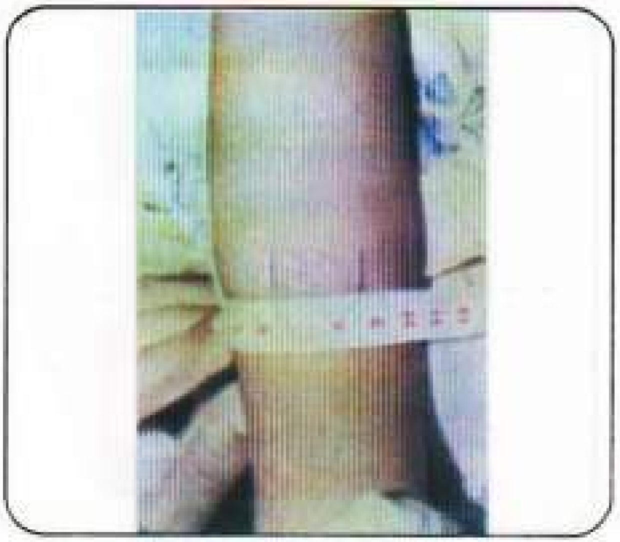
Icthyosis-toes erosion



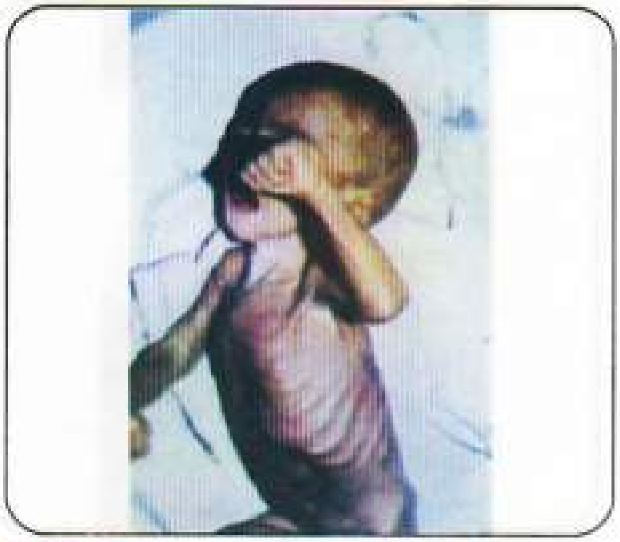
Icthyosis-extreme skin lesions.



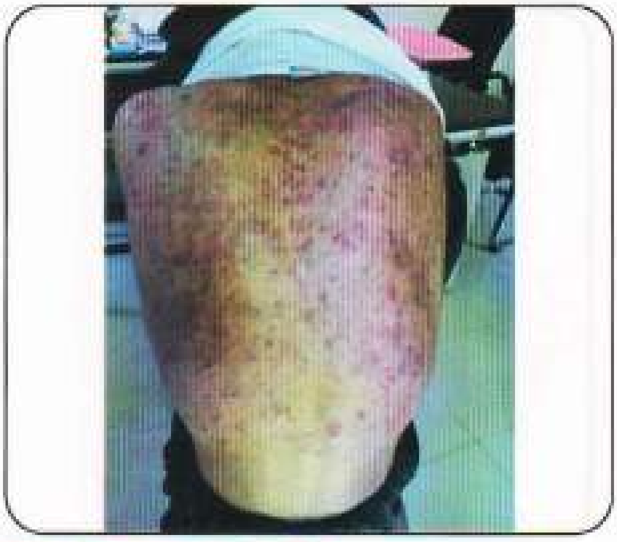
CT scan brain: Hydrocephalus.



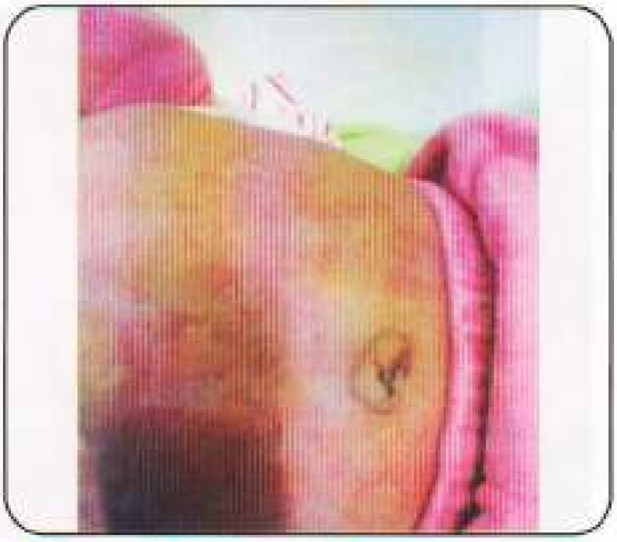
Mantoux test



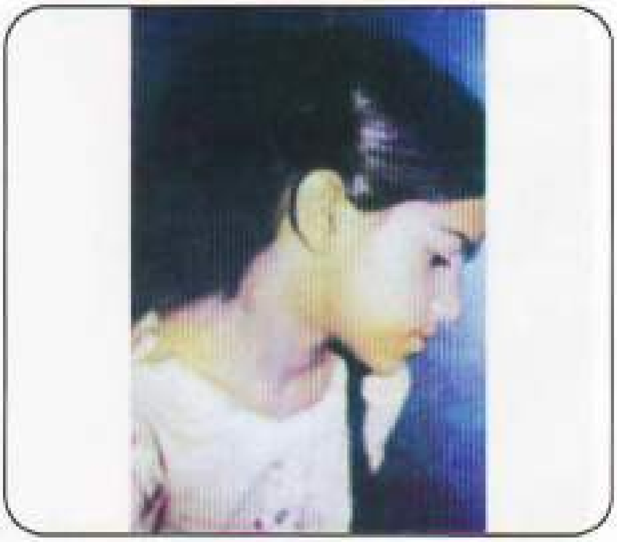
Marasmus.



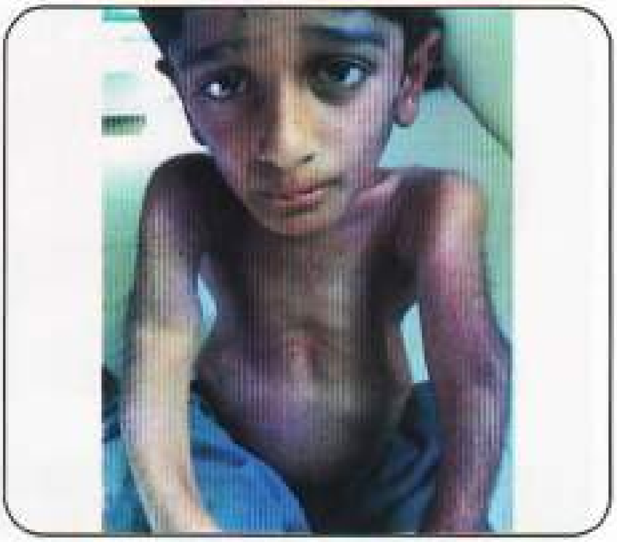
Infected scabies rash on the back



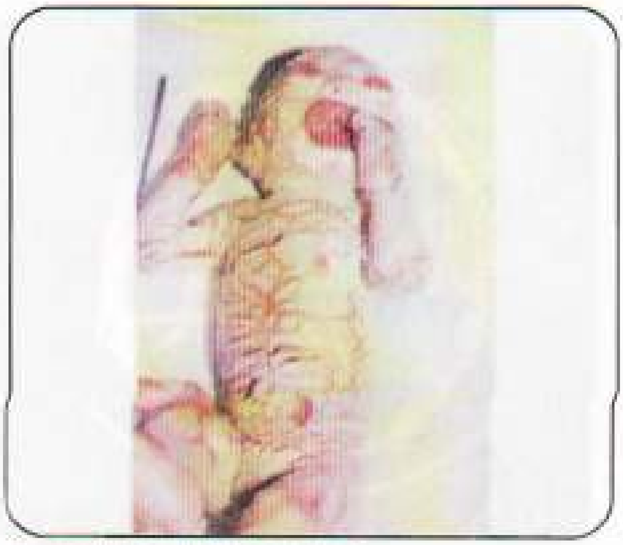
Morbilliform rash on abdominal wall



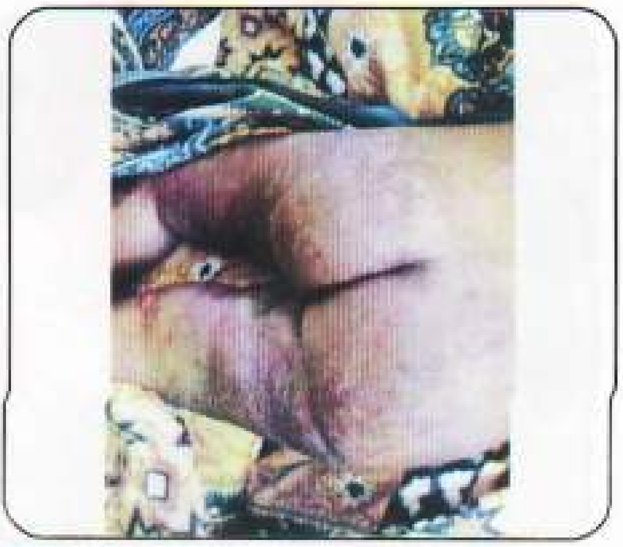
Cervical Lymphadenopathy



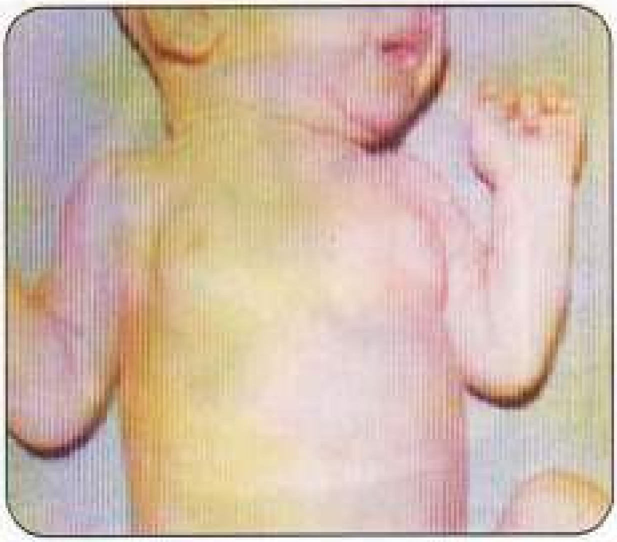
Chest deformity



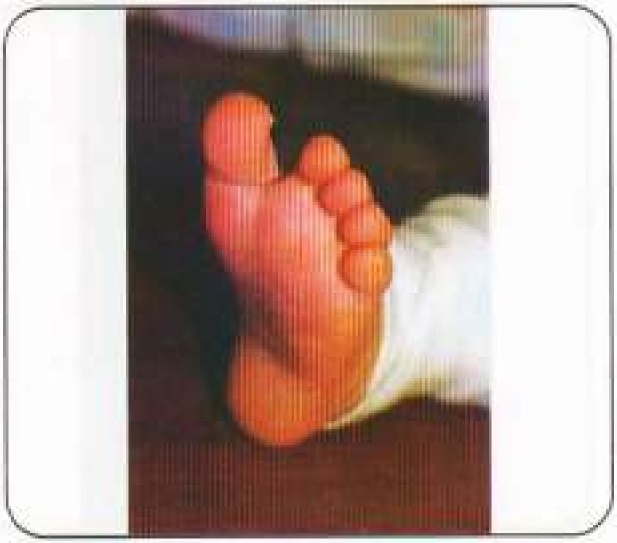
Congenital icthyosis (Harlequin fetus)



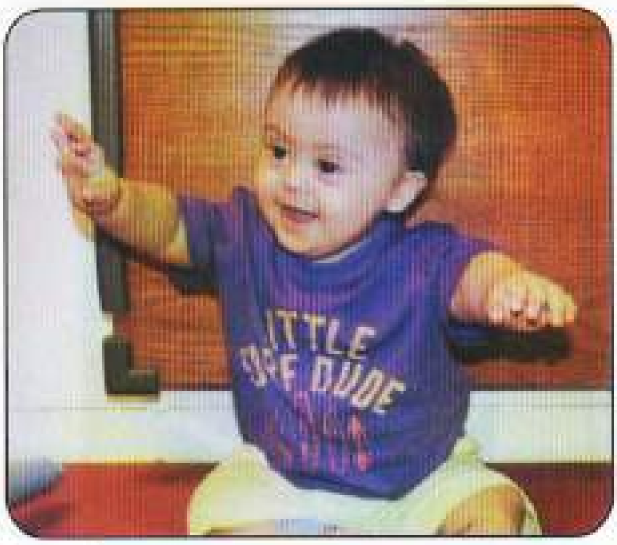
Extensive skin erosions on buttocks in persistent diarrhea



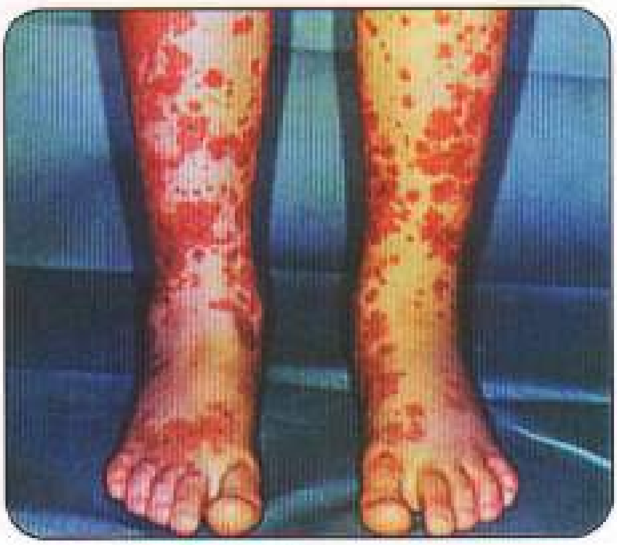
Gynecomastia in neonate



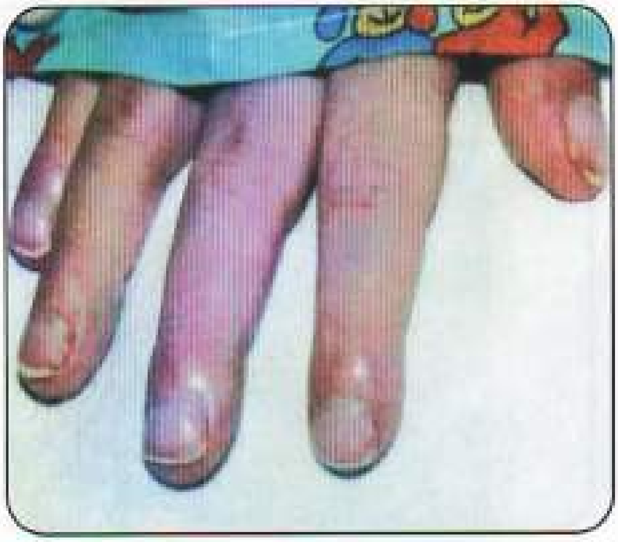
Down syndrome



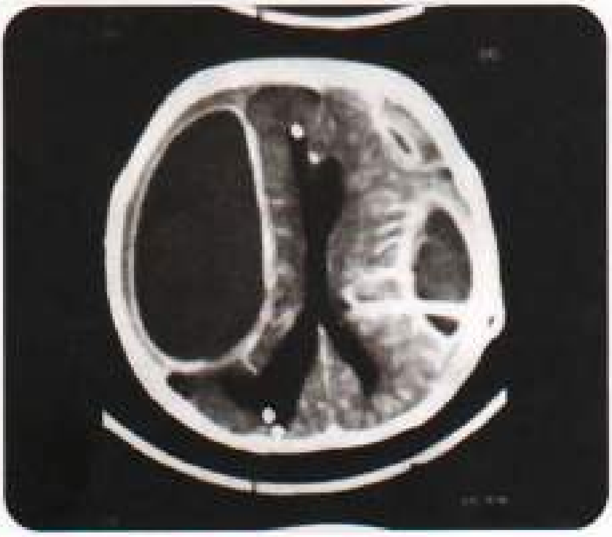
Down syndrome



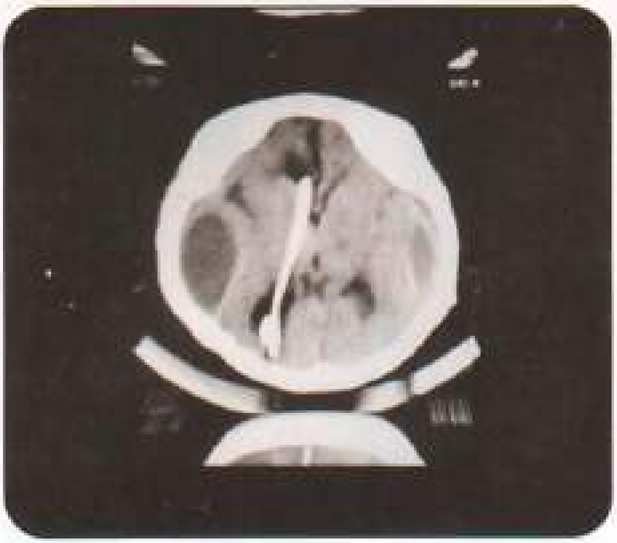
Henoch-Schonlein Purpura (HSP)



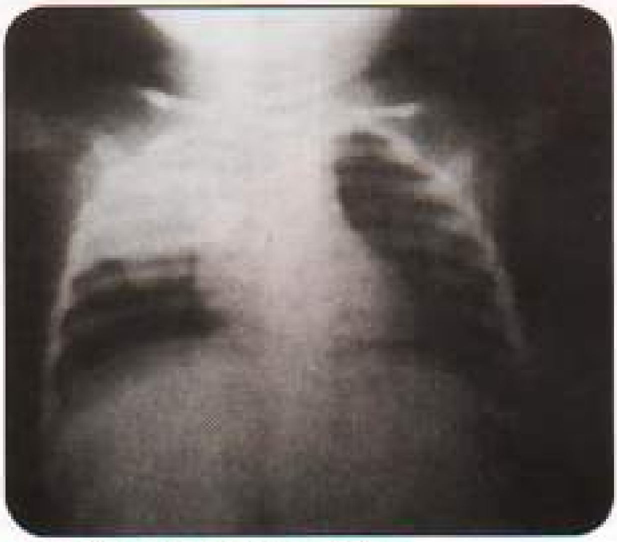
Cyanosis and finger clubbing in TOF



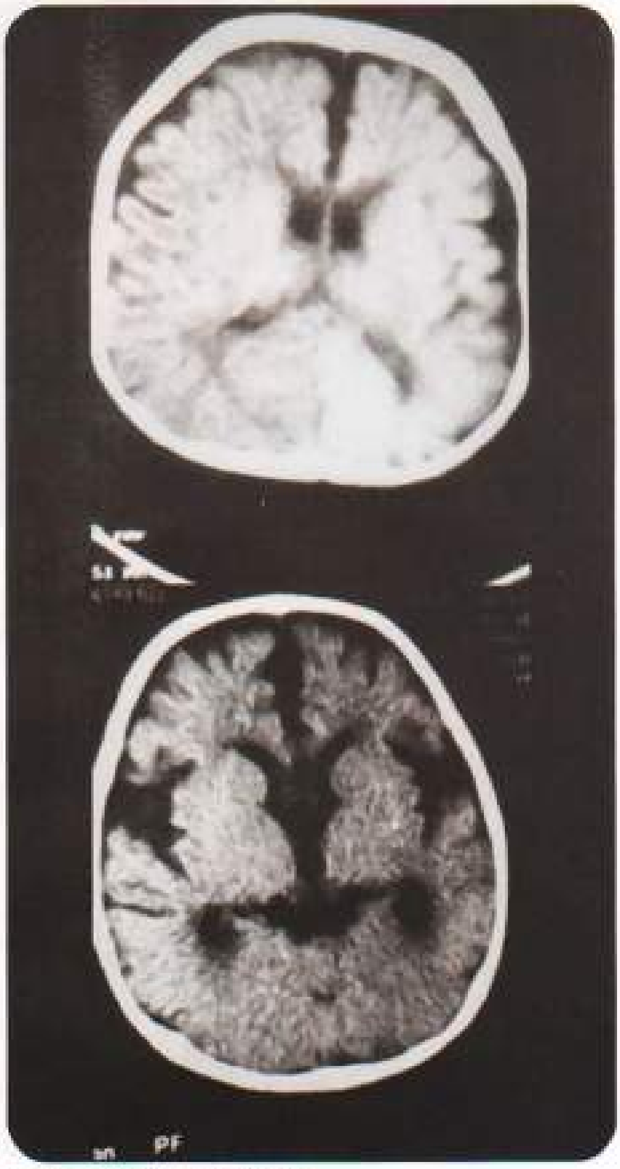
CT scan brain showing ring enhancing lesions (Brain abscess)



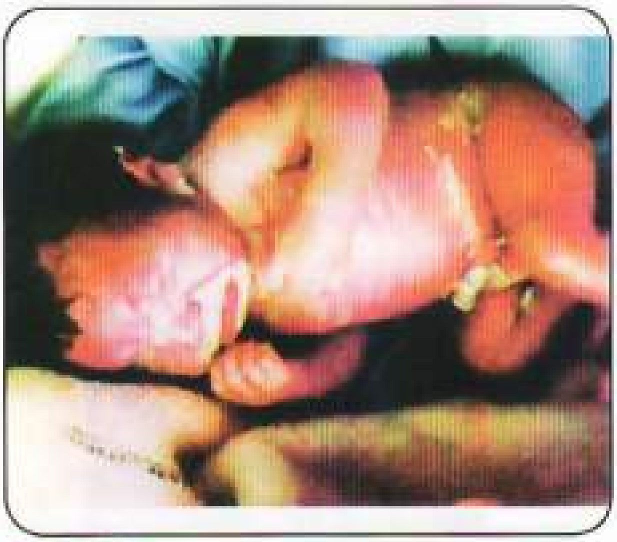
VP shunt in a case of hydrocephalus.



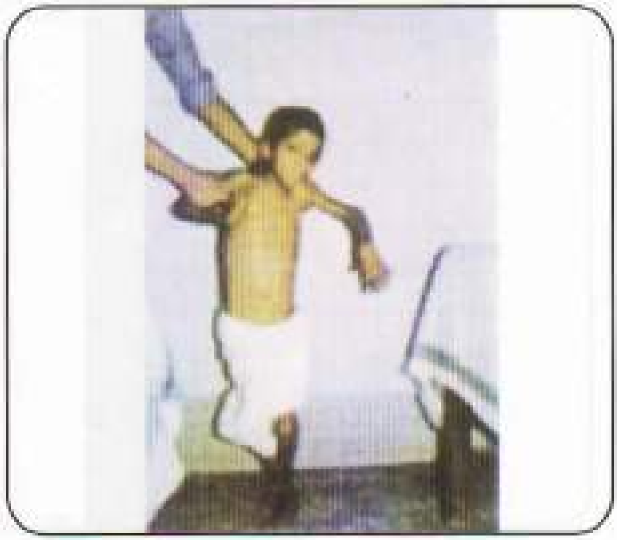
X-ray chest: Right-sided lobar pneumonia.



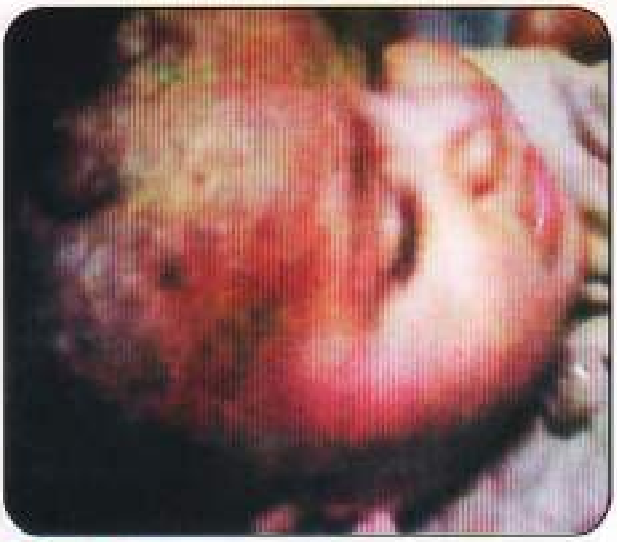
CT scan brain: Cerebral atrophy.



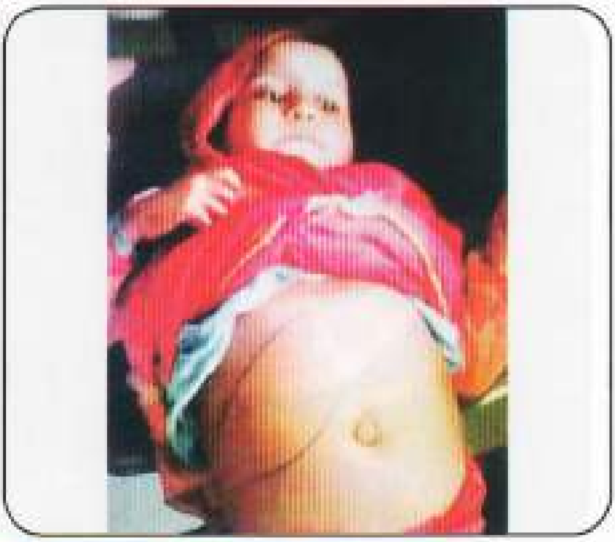
Collodion baby.



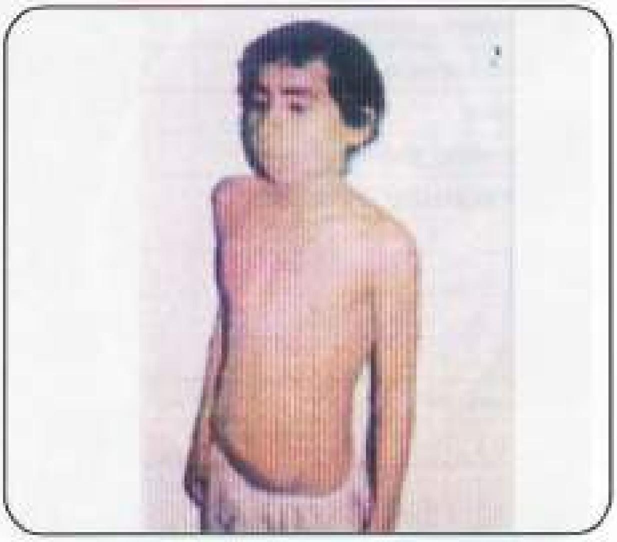
Cerebral Palsy.



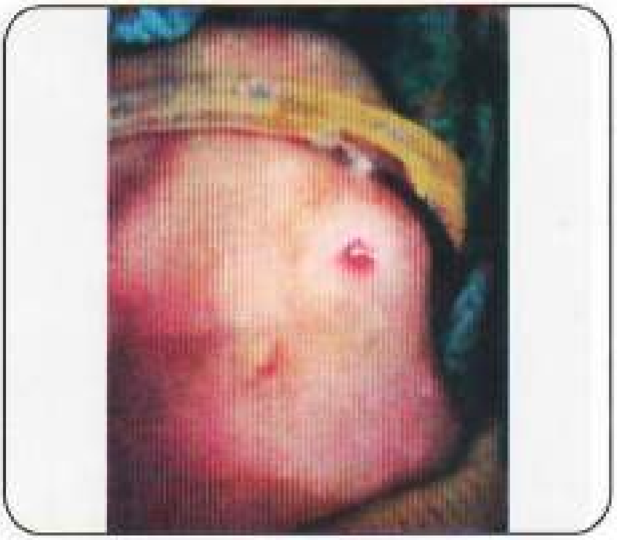
Eczema head



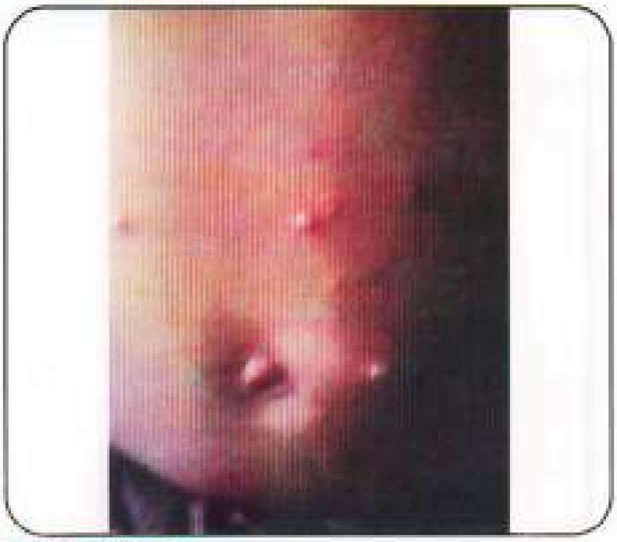
Hepatomegaly in glycogen storage disease.



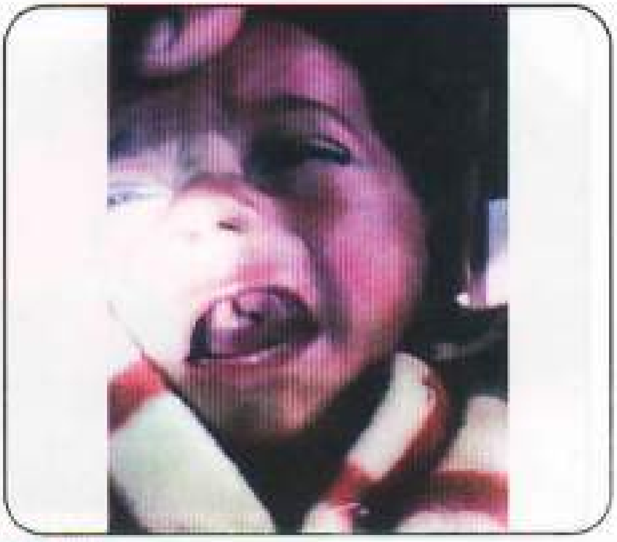
Increased anteroposterior diameter of the chest in a patient with bronchial asthma.



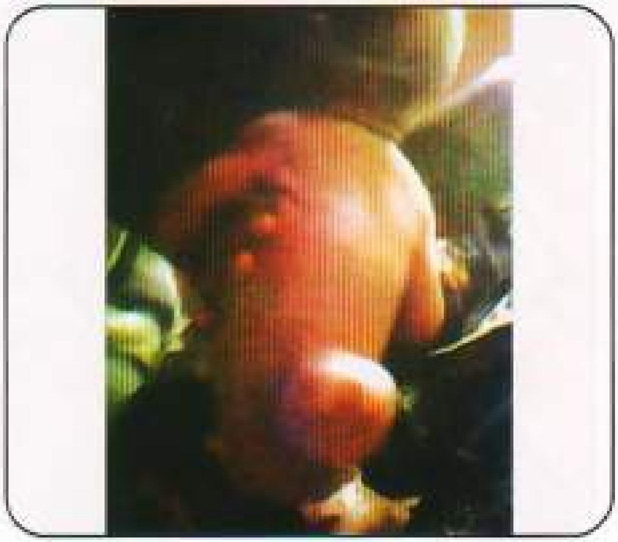
Mark after removing gastrostomy tube.



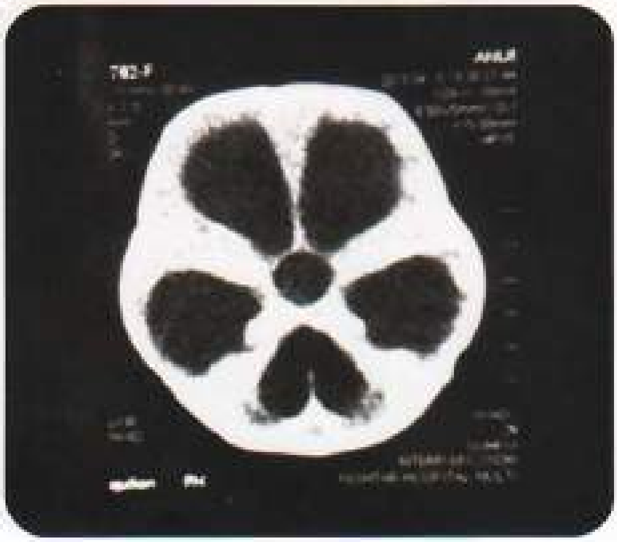
Rash of chicken pox



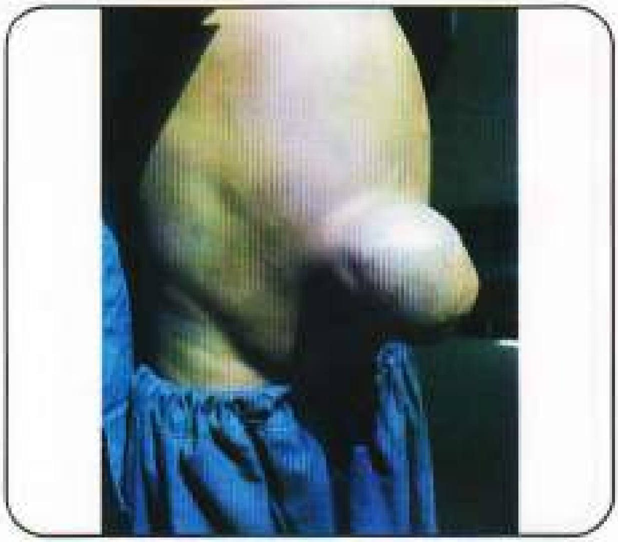
Cleft palate



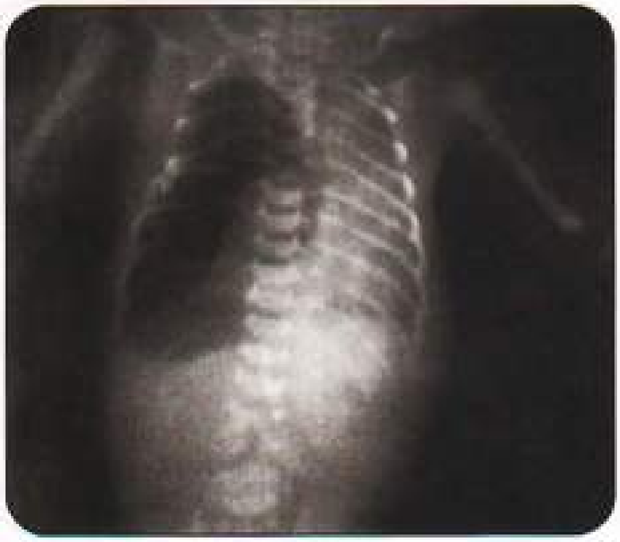
Meningomyelocele.



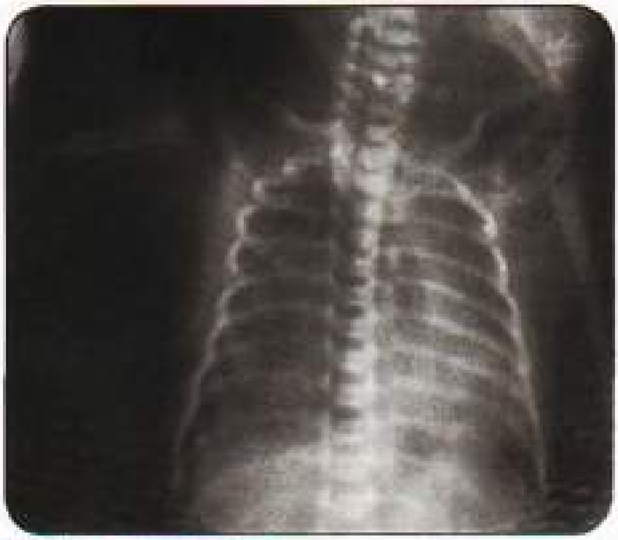
CT scan brain: Hydrocephalus.



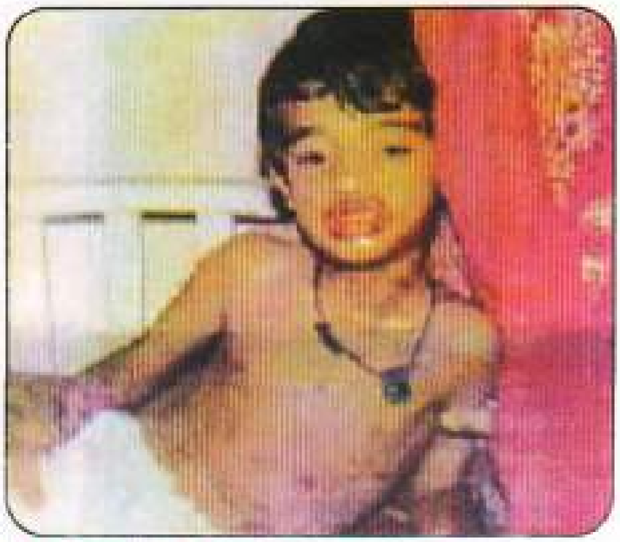
Umbilical hernia



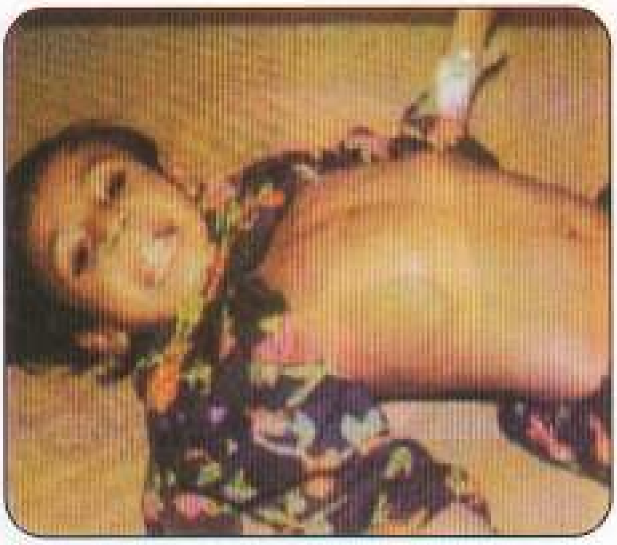
Pneumothorax.



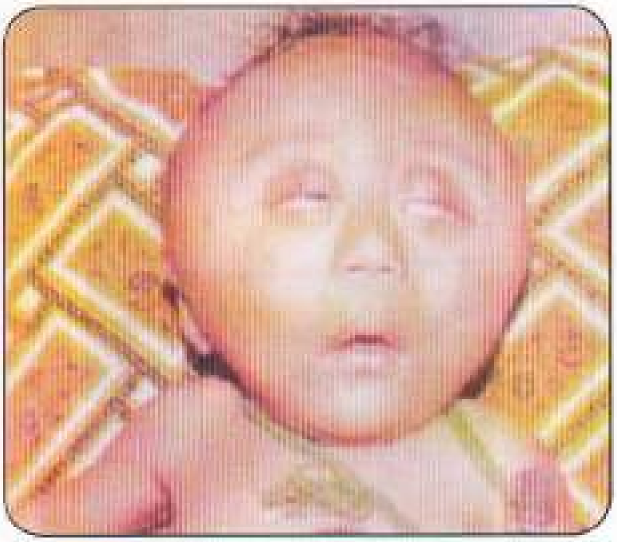
Chest tube in pneumothorax.



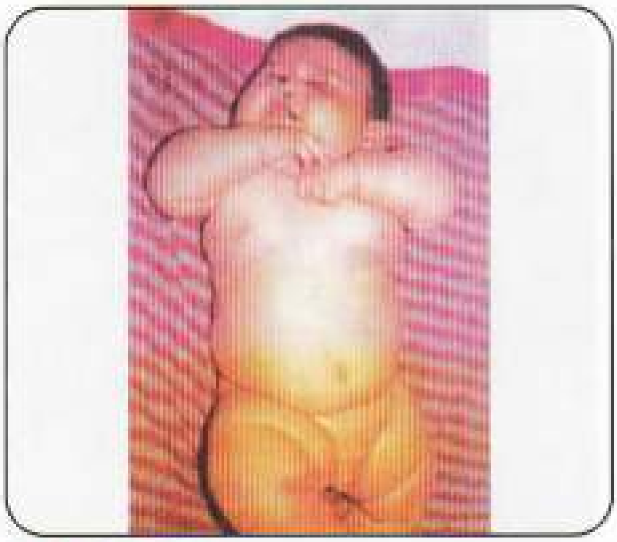
Mouth ulceration in Steven Johnson syndrome.



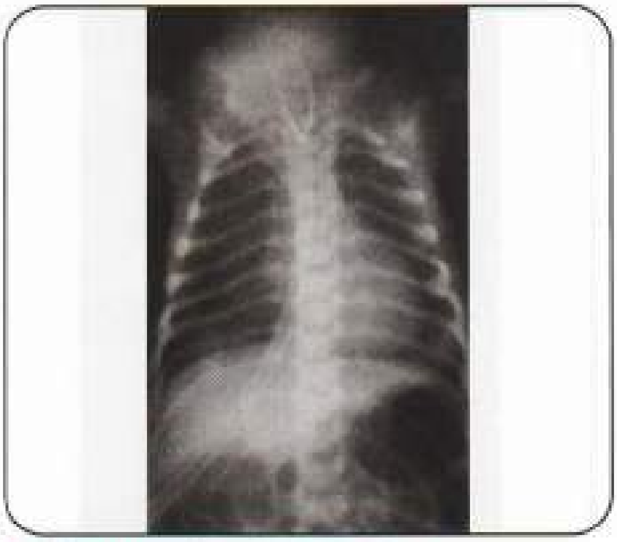
Tetanus.



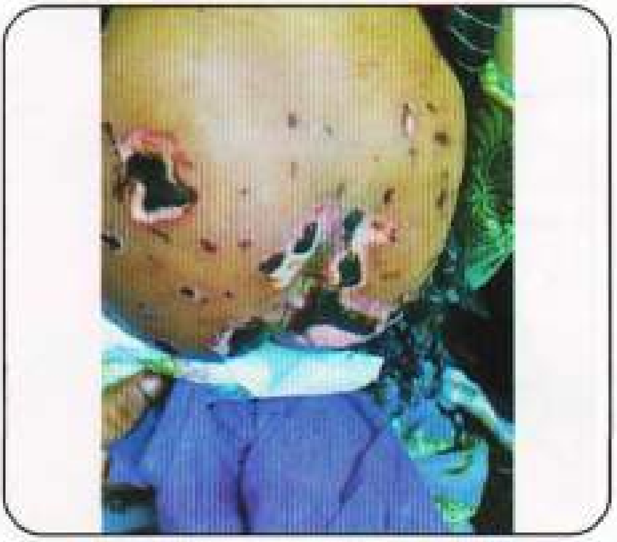
Anencephaly.



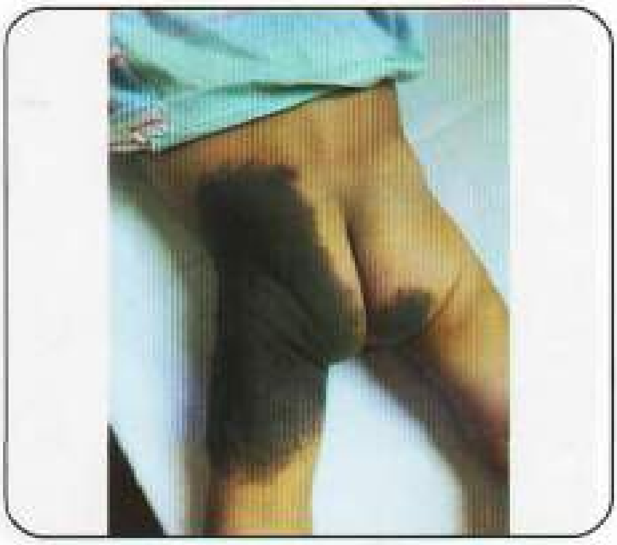
Large for dates baby.



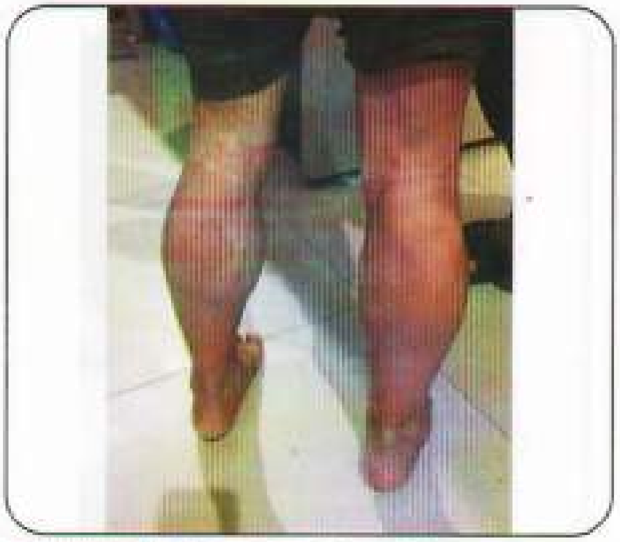
NG tube not passed in esophageal atresia.



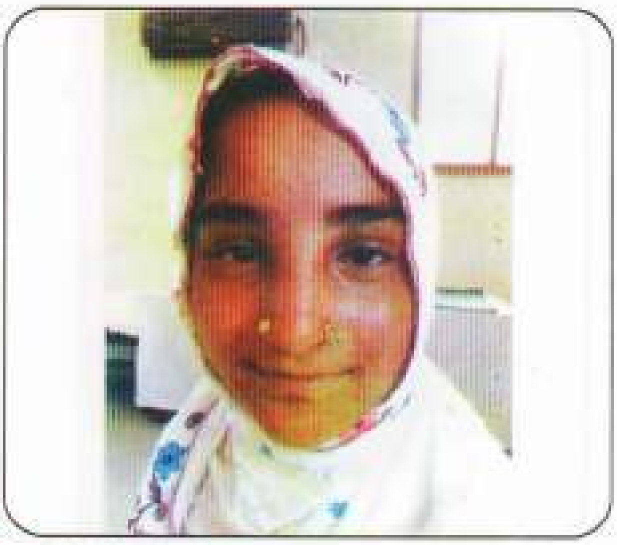
Necrotic ,punched out lessons in abdominal infection.



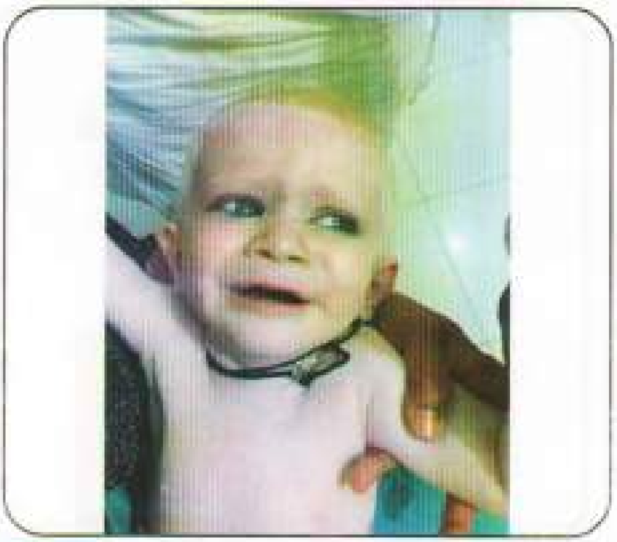
Birth mark-skin blackening.



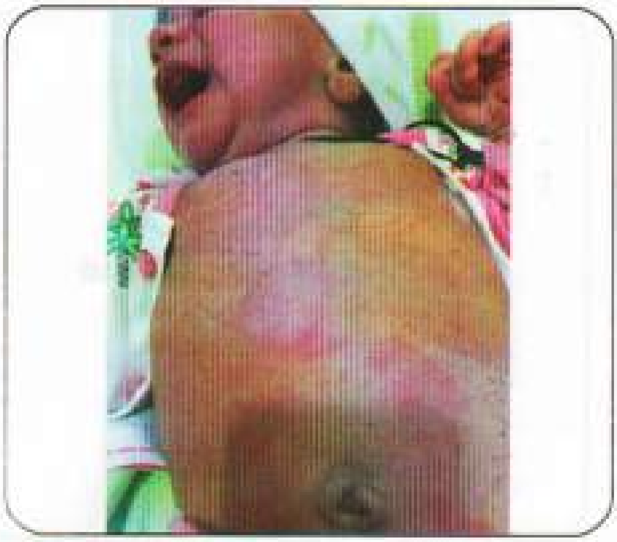
Calf hypertrophy duchenne muscular dystrophy



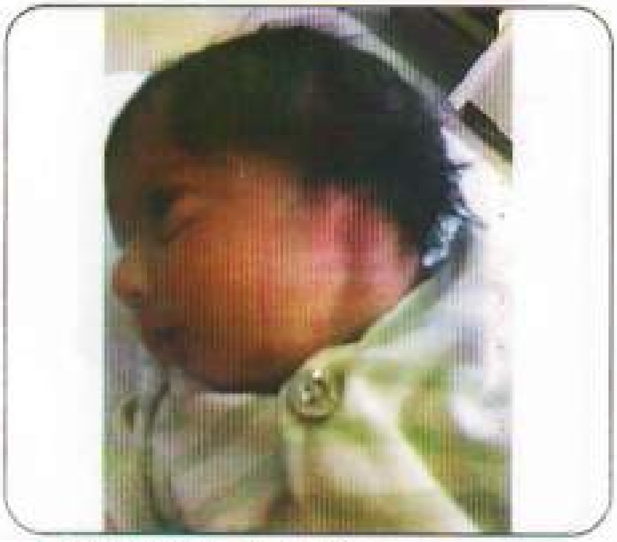
SLE patient on steroids



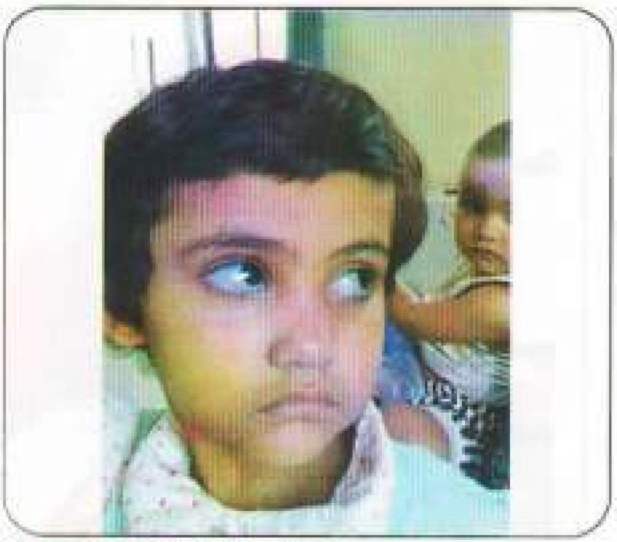
Albinism



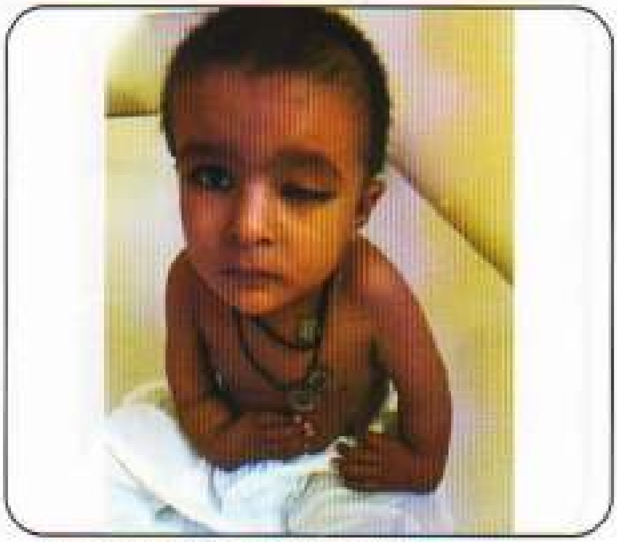
Neonatal erythema



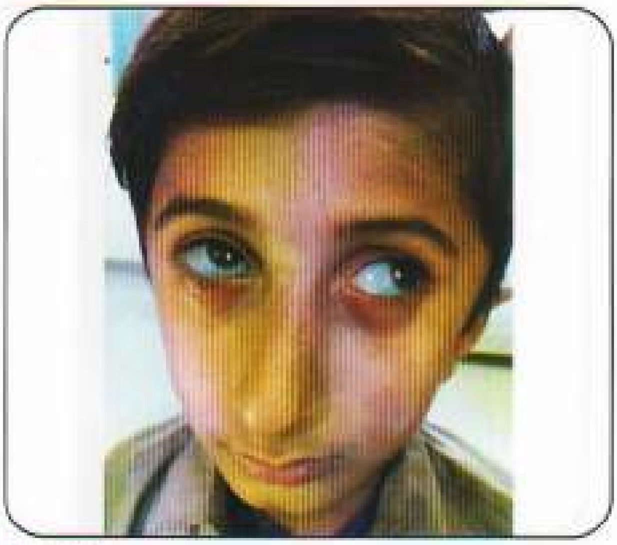
Sternomastoid tumor-newborn.



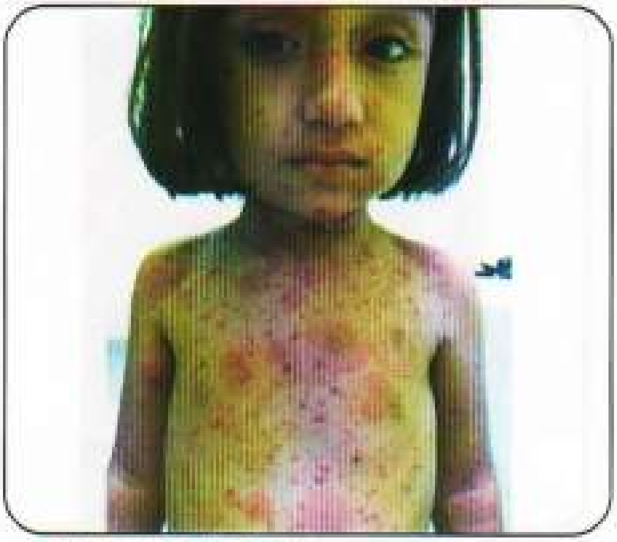
Blue sclera in Ectodermal dysplasia



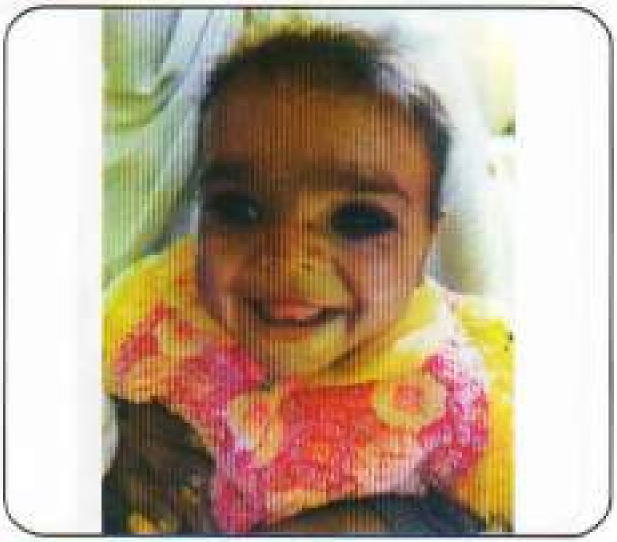
Thrombocytopenia with Tarr syndrome



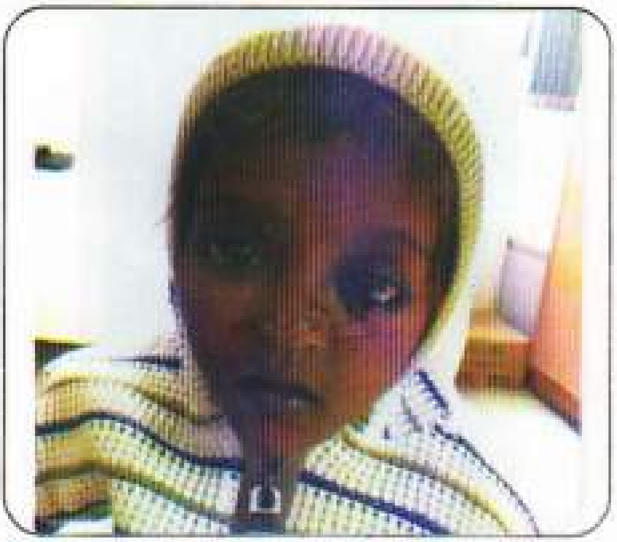
Blue sclera



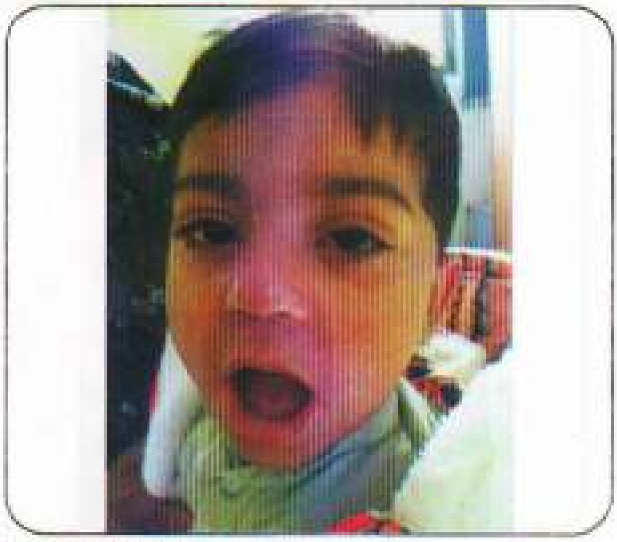
Staphlococcal skin infection



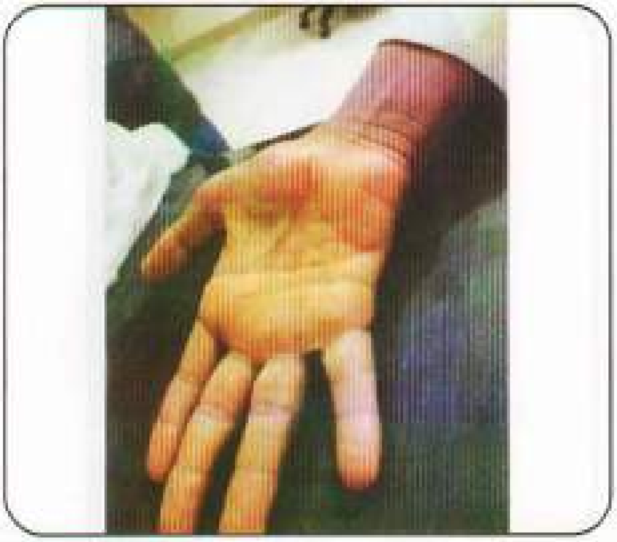
Hypothyroid baby with coarse facies



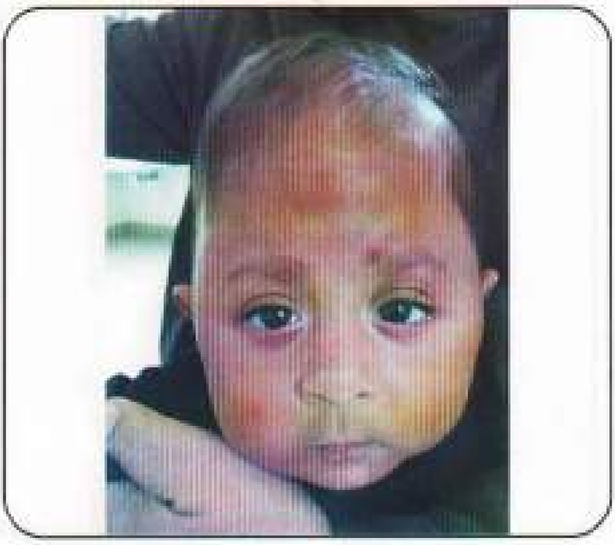
Blackening in Addison's disease



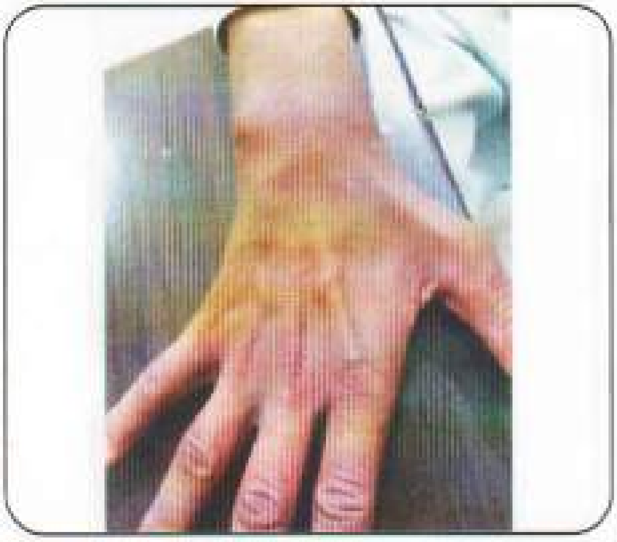
Measles rash on face



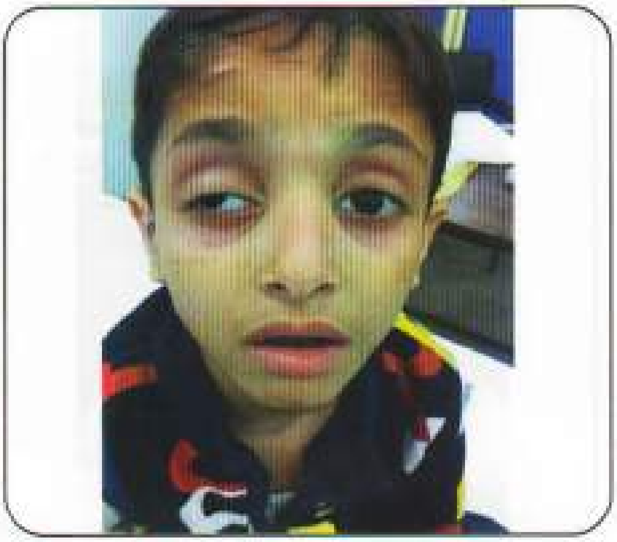
Thenar and hypothenar atrophy



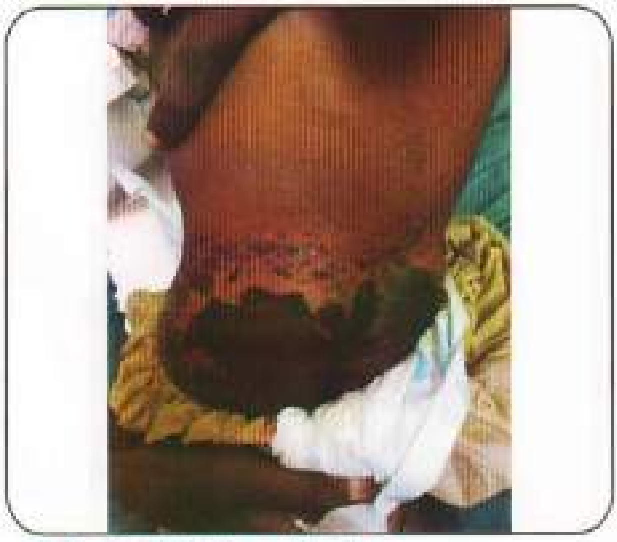
Conical forehead



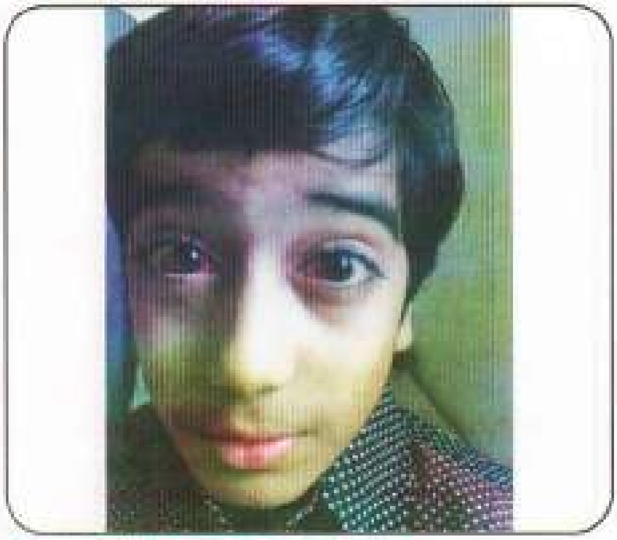
Wasting of interossei muscles



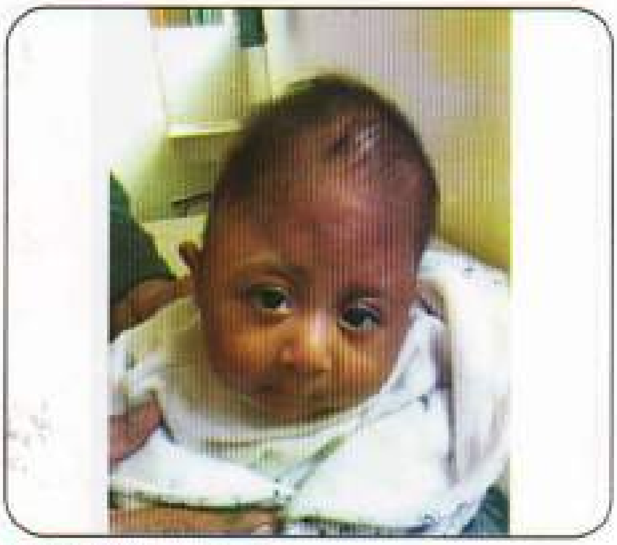
Congenital ptosis-right



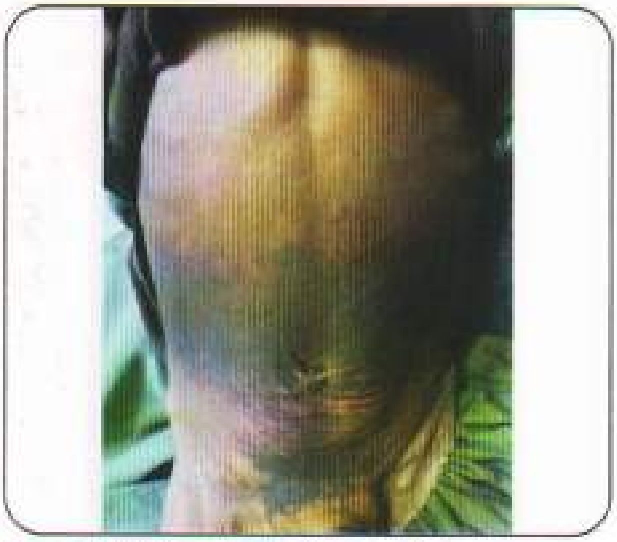
Sepsis-skin blackening and scaling



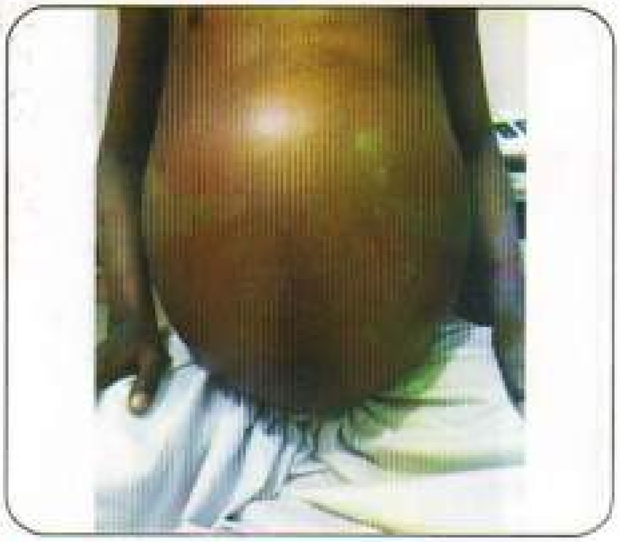
Subconjunctival haemorrhages in pertussis



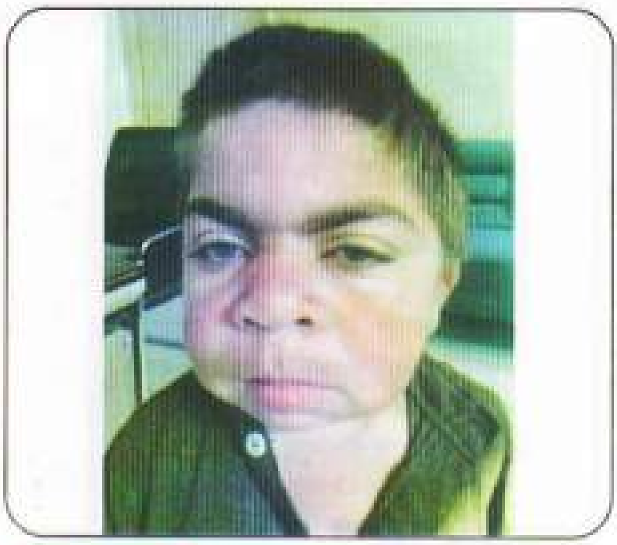
Towering skull in oxycephaly



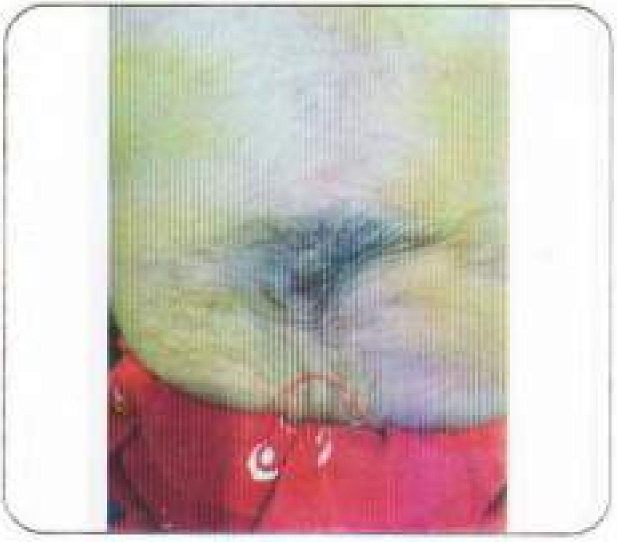
Blackening of abdominal wall in low grade DIC



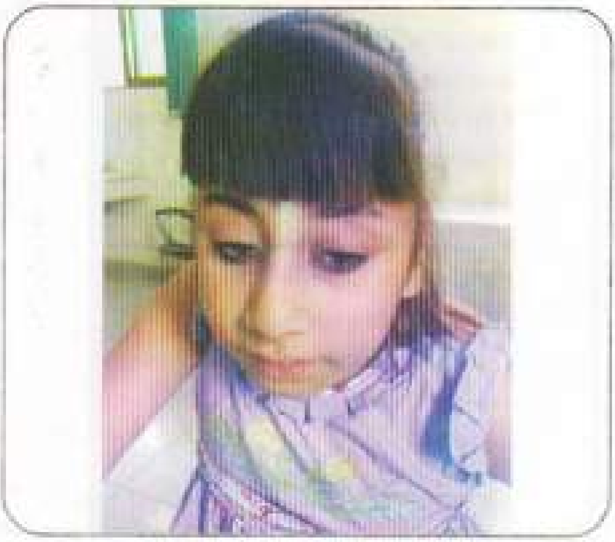
Gross ascites in cirrhosis



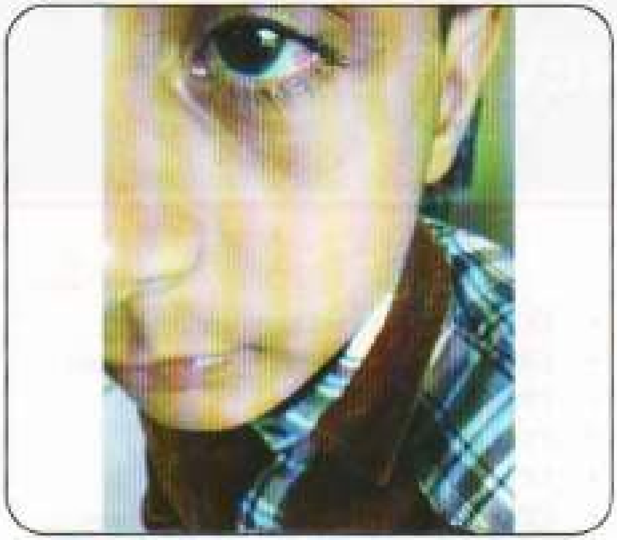
Coarse facies in Mucopolysaccharidosis



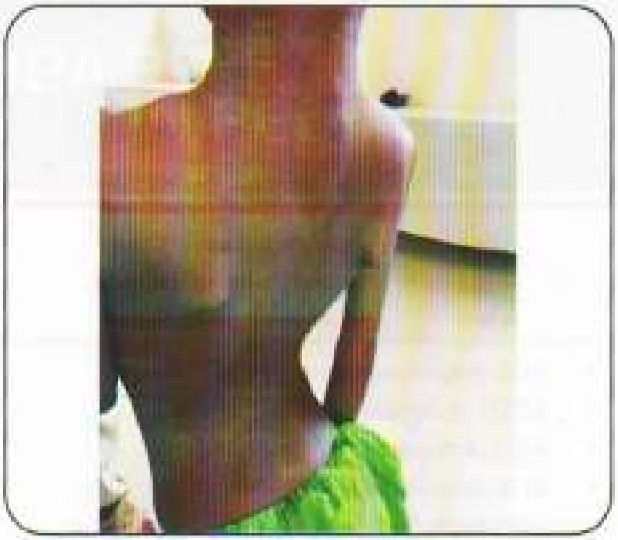
Sacral tuft of hairs in spinal dysraphism



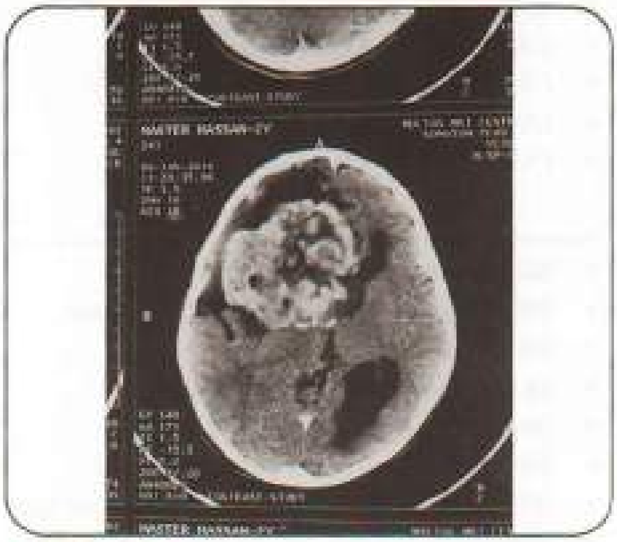
Microcephaly



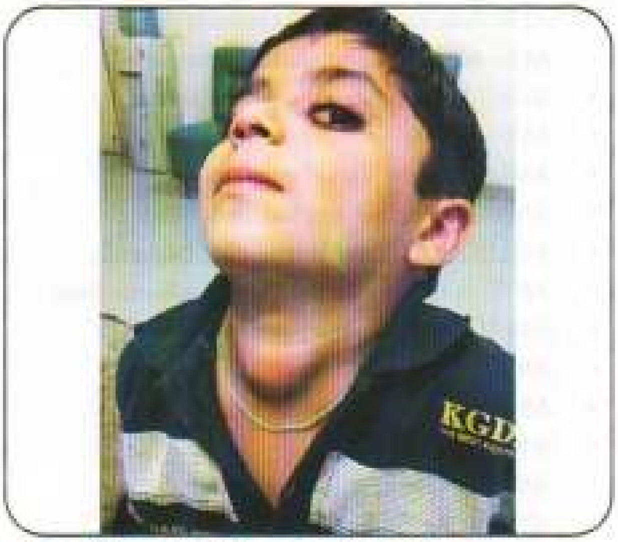
Telengictasia



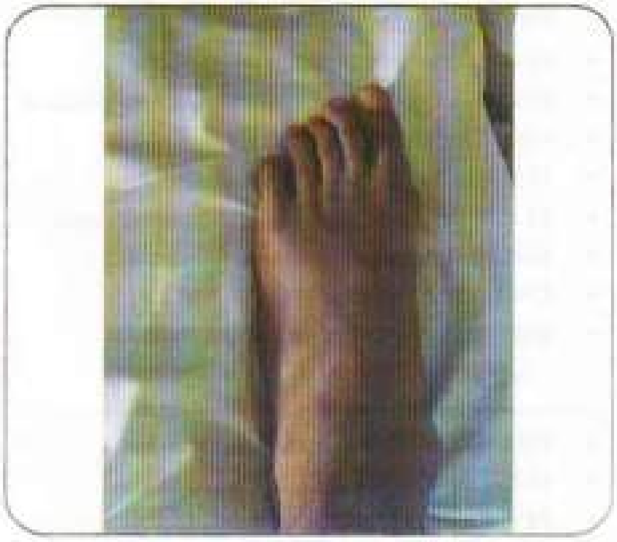
Muscular dystrophy -winging of scapula



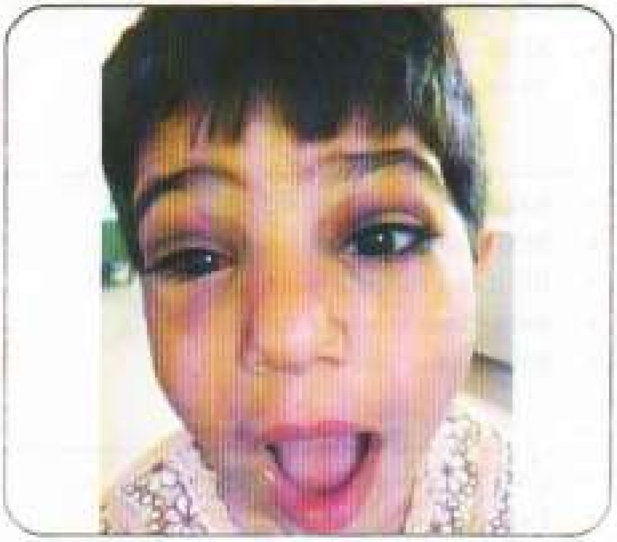
Brain tumour



Thyroiditis-enlarged thyroid with erythema



Rheumatoid arthritis



Subconjuctival haemorrhage in pertussis

LIST OF ABBREVIATIONS

A

- ACE–Angiotensin Converting Enzyme
- ACTH–Adrenocorticotropic Hormone
- ADH–Antidiuretic Hormone
- AFB–Acid-Fast Bacilli
- AFP–Acute Flaccid Paralysis
- AGA–Appropriate for Gestation
- AGN–Acute Glomerulonephritis
- ALG–Anti-Lymphocytic Globulin
- ALL–Acute Lymphoblastic Leukemia
- ALRI–Acute Lower Respiratory Infections
- ALT–Alanine Aminotransferase
- AML–Acute Myeloid Leukemia
- ANA–Antinuclear Antibodies
- ANLL–Acute Non-Lymphocytic Leukemia
- APTT–Activated Partial Thromboplastin Time
- ARI–Acute Respiratory Infections
- ARF–Acute Renal Failure
- ASD–Atrial Septal Defect
- ASO–Antistreptolysin O
- AST–Aspartate Aminotransferase
- ATN–Acute Tubular Necrosis
- ATG–Anti-Thymocytic Globulin
- ATS–Antitoxin Tetanus (Horse) Serum
- ATT–Antituberculous Therapy
- AURI–Acute upper respiratory infections
- AV–Atrioventricular

B

- BAL–British Anti Lewisite
- BCG–Bacille Calmette Guerin
- BD–Twice Daily (in two divided doses)
- BMR–Basal Metabolic Rate
- BT–Bleeding Time

C

- CAH–Congenital Adrenal Hyperplasia
- Cal–Calories
- CBC–Complete Blood Count
- CCF–Congestive Cardiac Failure
- CIE–Countercurrent Immuno-Electrophoresis
- CMV–Cytomegalovirus
- CO–Carbon Monoxide
- CP–Cerebral Palsy
- CPAP–Continuous Positive Airway Pressure
- CPK–Creatinine Phospho-Kinase
- CRF–Chronic Renal Failure
- CSF–Cerebrospinal Fluid
- CAT–Computed Axial Tomography
- CT–Clotting Time
- CVA–Cerebrovascular Accident
- CVS–Chorionic Villus Sampling

D

- DDAVP–Desmopressin Acetate
- DIC–Disseminated Intravascular Coagulation
- DKA–Diabetic Ketoacidosis
- DLC–Differential Leukocyte Count
- DMSA–Dimercapto-Succinic Acid Scan
- DPT–Diphtheria Tetanus Pertussis Vaccine
- DTPA–Diethylene Triamine Pentaacetic Acid Scan
- DW–Dextrose Water

E

- EBV–Epstein Barr virus
- ECG–Electrocardiogram
- ECMO–Extra-Corporeal Membrane Oxygenation
- EEG–Electroencephalogram
- EIA–Enzyme Linked Immunoassay
- ELISA–Enzyme Linked Immunosorbent Assay
- EMG–Electromyogram
- EN–Enteral Nutrition
- ESR–Erythrocyte Sedimentation Rate

F

- FDP–Fibrin Degradation Products
- FFA–Free Fatty Acids
- FFP–Fresh Frozen Plasma
- FRC–Functional Residual Capacity

G

- G6PD–Glucose-6-phosphate dehydrogenase
- GABA–Gammaaminobutyric Acid
- GBS–Guillain-Barre Syndrome
- GCS–Glasgow Coma Scale
- GFR–Glomerular Filtration Rate
- GIT–Gastrointestinal Tract
- GM-CSF–Granulocyte Macrophage Colony Stimulating Factor
- GN–Glomerulonephritis
- GSD–Glycogen Storage Disease

H

- HAV–Hepatitis A virus
- Hb–Hemoglobin
- HbA–Adult hemoglobin
- HbF–Fetal hemoglobin
- HBIG–Hepatitis B Immunoglobulin
- HBV–Hepatitis B Virus
- HbsAg–Hepatitis B surface antigen
- HCV–Hepatitis C Virus
- HDCV–Human Diploid Cell Vaccination
- HDV–Hepatitis D Virus
- HEV–Hepatitis E Virus
- HFV–Hepatitis F Virus
- HGV–Hepatitis G Virus
- Hib–H. influenzae type b
- HIE–Hypoxic Ischemic Encephalopathy
- HIV–Human Immunodeficiency Virus
- HLA–Human Leukocyte Antigen.
- H/O–History of
- HSP–Henoch-Schonlein Purpura
- HSV–Herpes Simplex Virus
- HTLV–Human T cell Lymphotropic Virus.
- HUS–Hemolytic Uremic Syndrome.

I

- IBD–Inflammatory Bowel Disease
- ICP–Intracranial Pressure
- ICT–Immunochromatographic Test.
- IDDM–Insulin Dependent Diabetes Mellitus
- IDM–Infant of Diabetic Mother
- Ig–Immunoglobulin
- IM–Intramuscular
- IMCI–Integrated Management of Childhood Illness
- INF–Interferon
- INH–Isoniazid
- IPV–Injectable Poliovirus Vaccine (Salk).
- IPPV–Intermittent Positive Pressure Ventilation
- IQ–Intelligence Quotient
- IRDS–Idiopathic Respiratory Distress Syndrome
- ITP–Idiopathic Thrombocytopenic Purpura
- IU–International Units
- IUGR–Intrauterine Growth Retardation
- IV–Intravenous
- IVIG–Intravenous Immunoglobulin
- IVH–Intraventricular Hemorrhage
- IVP–Intravenous Pyelography

K

- KCl–Potassium Chloride
- KF–Kayser Fleischer Rings
- Kg–Kilogram

L

- LBW–Low Birth Weight
- LDH–Lactate Dehydrogenase
- LDL–Low-Density Lipoprotein
- LGA–Large for Gestation
- LFT–Liver Function Test
- LP–Lumbar Puncture

M

- MCV–Mean Corpuscular Volume
- MCH–Mean Corpuscular Hemoglobin
- MCHC–Mean Corpuscular Hemoglobin Concentration
- MCU–Micturating Cystourethrogram
- MMR–Measles Mumps Rubella Vaccine
- MP–Malarial Parasite
- MPS–Mononuclear Phagocyte System/ Mucopolysaccharidoses
- MRI–Magnetic Resonance Imaging
- MU–Million Units

N

- NaCl–Sodium Chloride
- NADPH–Nicotinamide Adenine Dinucleotide
- NEC–Necrotizing Enterocolitis
- NG–Nasogastric Tube
- NICU–Neonatal Intensive Care Unit
- NO–Nitrous Oxide
- NPO–Nothing Per Oral
- NS–Nephrotic Syndrome
- NSAID–Non Steroidal Anti-inflammatory Drugs

O

- OD–Once Daily

- OLT–Orthotopic Liver Transplantation
- OPV–Oral Poliovirus Vaccine (Sabin)
- ORS–Oral Rehydration Salt
- Oz–Ounce

P

- PaO_2–Partial Pressure of Oxygen
- PCR–Polymerase Chain Reaction
- PDA–Patent Ductus Arteriosus
- PEFR–Peak Expiratory Flow Rate
- PEM–Protein Energy Malnutrition
- PGE–Prostaglandin E
- PN–Parenteral Nutrition
- PO–Per Oral
- PPD–Purified Protein Derivative
- PROM–Prolonged Rupture of Membranes
- PT–Prothrombin Time
- PTH–Parathyroid Hormone
- PUO–Pyrexia of Unknown Origin
- PZA–Pyrazinamide

Q

- QOD–Every Other Day, On Alternate Day

R

- RAST–Radioallergosorbent Testing
- RBC–Red Blood Cells
- RDA–Recommended Daily Allowance
- RDS–Respiratory Distress Syndrome
- RDW–Red cell Distribution Width
- RIBA–Recombinant Immunoblot Assay
- RPGN–Rapidly Progressive Glomerulonephritis
- RSV–Respiratory Syncytial Virus
- RTA–Renal Tubular Acidosis
- RV–Residual Volume

S

- SaO_2–Oxygen Saturation
- SC–Subcutaneous
- SD–Standard Deviation
- SE–Serum Electrolytes
- SGA–Small for Gestation
- SGOT–Serum Glutamic-Oxaloacetic Transaminase
- SGPT–Serum Glutamate Pyruvate Transaminase
- SIADH–Syndrome of Inappropriate Antidiuretic Hormone
- SLE–Systemic Lupus Erythematosis
- SMA–Spinal Muscular Atrophy
- SOL–Space Occupying Lesion
- SSPE–Subacute Sclerosing Panencephalitis

T

- T_4–Thyroid Hormone
- TB–Tuberculosis
- TBM–Tuberculous Meningitis
- TDS–Three Times Daily
- TGA–Transposition of Great Arteries
- TIBC–Total Iron Binding Capacity
- TIG–Tetanus Immunoglobulin (Human)
- TIPS–Transjugular Intrahepatic Portosystemic Shunt
- TLC–Total Leukocyte Count/Total Lung Capacity
- TNF–Tissue Necrosis Factor
- TOF–Tetralogy of Fallot
- TORCH–Toxoplasmosis, Others (such as syphilis, hepatitis B), Rubella, Cytomegalovirus, and Herpes Simplex Virus
- TPN–Total Parenteral Nutrition
- TRH–Thyrotropin-Releasing Hormone
- TSF–Teaspoonful
- TSH–Thyroid Stimulating Hormone
- TT–Tetanus Toxoid
- TTN–Transient Tachypnea of Newborn

U

- USG–Ultrasonography
- UTI–Urinary Tract Infection
- UV–Ultraviolet

V

- VACTERAL–Vertebral, Anorectal, Cardiac, Tracheoesophageal, Renal, and Limb Anomalies
- VAPP–Vaccine Associated Paralytic Poliomyelitis
- VC–Vital Capacity
- VCUG–Voiding Cystourethrography
- VLBW–Very Low Birth Weight
- VP shunt–Ventriculoperitoneal Shunt
- VSD–Ventricular Septal Defect
- VUR–Vesicoureteral Reflux
- VWF–Von Willebrand's Factor
- VZV–Varicella Zoster Virus
- VZIG–Varicella Zoster Immunoglobulin

W

- WBC–White Blood Cell Count
- WHO–World Health Organization

Z

- ZN stain–Ziehl-Neelsen Stain

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